REMARKS

Claims 1-6, 9-18, 20-28, 30, 32-35 and 39-74 are pending.

Claim 9 has been made independent of claim 6, which should result in no narrowing in the scope of the amended recitation. Claims 70-74, which correspond to claims 11-15 dependent on claim 6, have been added to ultimately depend on claim 9. Descriptive support for the new claims 70-74 can be found in the specification at page 4, line 16 to page 5, line 1; page 5, lines 8-10 and 16-27; page 7, lines 2-5; page 8, lines 1-12 and 25-27.

The amendment to claim 12 should not narrow the scope of the amended recitation because it is clear to a person skilled in the art that "the torsemide modification II" recited in claim 12 as originally filed refers to "the torsemide modification II" in the recitation of "wherein the torsemide modification II is selected from the group consisting of" in claim 11. The amendment to claim 12 also should not narrow the scope of the amended recitation because it is also clear to the person skilled in the art that "wherein the torsemide modification II comprises about 0.5 to about 2% (w/w) of torsemide modification I" recited in claim 12 as originally filed means the same thing as "wherein the torsemide modification II is torsemide modification II containing torsemide modification I at trace amounts" because "torsemide modification II containing torsemide modification I at trace amounts" is defined in claim 11 as torsemide modification II containing about 0.5 to about 2% (w/w) of torsemide modification I.

The amendment to claim 32 has been done to correct an antecedent basis issue involving "the high purity torsemide modification II". The dependency of claim 32 was changed from claim 31 to claim 28 in the Amendment filed on April 12, 2005, with the cancellation of claim 31. In the Amendment filed on July 19, 2004, "the high purity torsemide modification II" in claim 31 was replaced with "the torsemide modification II". The deletion of "high purity" from "the high purity torsemide modification II" in claim 31 on July 19, 2004 and in claim 32 now would not narrow the scope of the amended claim recitation.

The deletion of "povidone NF" from claim 50 has been done to remove redundancy. According to the attached *National Formulary*, p. 2821, povidone NF is the same as povidone USP. Since "povidone USP" is also in the Markush list in claim 50, "povidone NF" is deemed redundant, the deletion of which should not narrow the scope of the amended recitation.

Support for the new claims 52-68 can be found in the specification at page 2, the last line, to page 3, line 8; page 4, line 16, to page 5, line 1; page 5, lines 8-17 and 24-27; page 7, lines 7-18; and page 8, lines 3-23.

The new claim 69 is supported by the description in page 12, lines 19-26, of the specification.

Claim Rejections -- 35 U.S.C. 112, Second Paragraph

Applicants respectfully traverse the rejection of claims 9, 11-15, 50 and 51 as indefinite.

Claim 9 was rejected as indefinite because the Office Action alleges that claim 9 does not further limit the parent claim 6. Applicants respectfully traverse the rejection. However, to advance prosecution, applicants have made claim 9 independent of claim 6.

Claims 11 and 12 were rejected as vague on the grounds that claim 12 does not further limit the parent claim 11. Applicants respectfully disagree. In claim 11, "the torsemide modification" in the pharmaceutical formulation is either high purity torsemide modification II or torsemide modification II containing torsemide modification I at trace amounts, wherein "trace amounts" is defined as "about 0.5 weight% to about 2 weight%" . In contrast, in claim 12, "the torsemide modification" in the pharmaceutical formulation is torsemide modification II containing about 0.5 weight% to about 2 weight % of torsemide modification I, i.e., containing torsemide modification I at trace amounts. Thus, the scope of "the torsemide modification II" in claim 12 is narrower than "the torsemide modification II" in claim 11. In other words, claim 12 as originally filed did further limit claim 11. However, to advance prosecution, applicants have amended claim 12 as suggested by Examiner Gollamudi (please see above).

Claims 50 and 51 were rejected as vague on the ground that NF in "lactose anhydrous NF, crospovidone NF..." was unclear and indefinite. Applicants respectfully disagree. The name of a substance designated with "NF" means that the substance complies with standards set forth in the National Formulary Official Monograph for that substance (e.g., see *The National Formulary*, United States Pharmacopeial Convention, Inc., Rockville, MD, 2003, pages 2677-2684, attached). Examples of the National Formulary Official Monographs for lactose anhydrous, crospovidone, microcrystalline cellulose and povidone are also attached (e.g., see *The National Formulary*, United States Pharmacopeial Convention, Inc., Rockville, MD, 2003, pages 2685, 2713, 2714, 2727, 2779, 2780 and 2821). Similarly, "povidone USP" in claim 50 means

povidone that complies with the standard set forth in the United States Pharmacopeia (e.g., see *The United States Pharmacopeia*, United States Pharmacopeial Convention, Inc., Rockville, MD, 2003, pages iii-xii, 13, 1519 and 1520, attached).

The Office Action indicates that "the high purity torsemide modification II" in claim 32 lacks antecedent basis. But claim 32 was not rejected as vague. Applicants assume that claim 32 was merely objected to by the Examiner. The deletion of "high purity" from "the high purity torsemide modification II" in claim 32 should overcome the antecedent basis issue.

Information Disclosure Statement

Once again, applicants request that the Examiner return a copy of the PTO-1449 Form filed as a part of an IDS deposited with the U.S. Postal Service on May 28, 2002 (shown in the USPTO Public PAIR as scanned into the computer on June 6, 2002) with his initials to acknowledge consideration of the prior art references cited therein. Similar requests were made in the Amendment filed on July 19, 2004 and the Amendment filed on April 12, 2005. For the convenience of the Examiner, copies of the IDS and PTO-1449 Form filed on May 28, 2002 are also attached.

Double Patenting Rejections

Applicants respectfully traverse the rejection of claims 16-51 over the claims of U.S. Patent No. 6,482,417 (US '417) under the doctrine of obviousness-type double patenting. To advance prosecution, however, a terminal disclaimer over US '417 would be filed after the Examiner has held that at least some of the claims are allowable. Applicants request that the obviousness-type double patenting rejection be held on abeyance.

Applicants also respectfully traverse the obviousness-type double patenting rejection of claim 1 over claims 81, 82 and 85-87 of U.S. Patent No. 6,465,496 (US '496). The Examiner took a position that claim 1 in the instant application would have been obvious over claims 81, 82 and 85-87 of US '496 because claims 81, 82 and 85-87, being of broader scopes, embrace claim 1 of a narrower scope, and because the pH adjustments recited in steps d and f of claim 1 "is an obvious skill to practitioner in the art." The Office Action errs in asserting that the instant claim 1 is encompassed by claims 81, 82 and 85-87 of US '496. The process of the instant claim 1 prepares torsemide modification II starting with adding **crude torsemide modification II** to a

mixture comprising acetonitrile and water, isolating **torsemide modification I** and suspending **torsemide modification I** in water. In contrast, the processes claims 81, 82 and 85-87 of US '496 prepare torsemide modification II starting with adding **amorphous torsemide** to water, or suspending **amorphous torsemide** in water. Adding **amorphous torsemide** to water, or suspending **amorphous torsemide** in water, does not encompass adding **crude torsemide modification II** to a mixture comprising acetonitrile and water, isolating **torsemide modification I** and suspending **torsemide modification I** in water. Following the steps in claims 81, 82 and 85-87 of US '496 would not necessarily lead to the process of the instant claim 1. This is the main reason why the obviousness double patenting rejection over US '496 should be withdrawn.

The obviousness type double patenting rejection of claim 1 over claims 81, 82 and 85-87 of US '496 is partially based on the Examiner's allegation that the pH adjustments recited in steps d and f of claim 1 "is an obvious skill to practitioner in the art." Applicants would like to emphasize that any obviousness-type double patenting rejection of the instant claim 1 over claims 81, 82 and 85-87 of US '496 requires the Examiner to demonstrate that claims 81, 82 and 85-87 of US '496 would render claim 1 obvious (see MPEP 804). For a genus according to claims 81, 82 and 85-87 of US '496 to render obvious a subgenus according to the instant claim 1, there must be suggestion in claims 81, 82 and 85-87 or in the art to guide a person of ordinary skill in the art to the subgenus of claim 1. However, there is no suggestion in the prior art or in claims 81, 82 and 85-87 to lead a person of ordinary skill in the art to adjust the pH of a solution of torsemide modification I in water to a pH of about 10 +/- 0.2 and adjusting the pH of a filtered solution of torsemide modification I in water at pH of about 10 +/- 0.2 to about 6.25 +/- 0.2. Without any suggestion to adjust the pH as recited in steps d and f of claim 1, this is another reason why claims 81, 82 and 85-87 would not have rendered claim 1 obvious.

Claim Rejections -- 35 U.S.C. 102

Applicants respectfully traverse the anticipatory rejection of claims 1, 6, 9-18, 20-28, 30, 32-35, 39 and 43-49 over US '496.

For the rejection, the Office Action relies upon Example 9 to convert torsemide modification II to torsemide modification I and Example 12 to convert torsemide modification I to torsemide modification II. Applicants submit that US '496 does not anticipate the method of

claim 1 because the two aims of Examples 9 and 12 are exactly opposite. The aim of Example 9 was to convert torsemide modification II to torsemide modification I, while the aim of Example 12 was to convert torsemide modification I to torsemide modification II.

Example 9

Starting Material		Product
Modification II	---------->	Modification I

Example 12

Starting Material		Product
Modification I	---------->	Modification II

US '496 does not disclose using the methods of Examples 9 and 12 sequentially. The only processes for making torsemide modification II disclosed in the Summary of the Invention of US '496 start with amorphous torsemide (column 4, lines 12-17 and 24-30), not starting with torsemide modification II. In the Detailed Description of the Invention of US '496 (column 10, lines 10 to 34), the section with the heading "Torsemide Modification II" is completely silent on preparing torsemide modification II by starting with torsemide modification II and going through torsemide modification I in the middle of the process to prepare torsemide modification II as the final product. To a person skilled in the art reading the disclosures of US '496, Examples 9 and 12 show two independent and separate processes for preparing two different polymorphs of torsemide (i.e., torsemide modification I in Example 9; and torsemide modification II in Example 12).

The Examiner stated that combining Examples 9 and 12 sequentially is implicit from the disclosure of US '496 "since clearly one needs torsemide modification I as derived from the previous examples for the process of isolating purified modification II." Applicants respectfully disagree because Example 12 does not state to use the torsemide modification I prepared in any of Examples 4 and 9-11 as the starting material and it is not clear that one needs to use torsemide modification II derived from any of Examples 4 and 9-11 as the starting material in Example 12.

Based on the disclosures of US '496, it is not clear or implicit that one would use torsemide modification I derived from Example 9 as the starting material in Example 12 because Example 9 started with torsemide modification II and Example 12 ended with torsemide modification II. In reading US '496, the person skilled in the art would not recognize that US '496 teaches an apparently laborious process of starting with torsemide modification II to prepare torsemide modification I as in Example 9 and then using the torsemide modification I of Example 9 as the starting material in Example 12 to prepare torsemide modification II. In addition, there is no indication anywhere in US '496 of any benefit of taking such an apparently laborious route (combining Examples 9 and 12 sequentially) to prepare torsemide modification II. Example 9 prepared torsemide modification I free of torsemide modification II, but US '496 does not indicate any need of using torsemide modification I free of torsemide modification II as the starting material in Example 12 in order to prepare torsemide modification II. The mere fact that Example 12 is one of the examples following Example 9 in US '496 does not necessarily mean that US '469 teaches a person skilled in the art to combine Examples 9 and 12 sequentially. Thus, in spite of Examples 9 and 12, US '496 does not anticipate claim 1.

Page 8 of the Office Action argues that because the processes of Examples 9 and 12 of US '469 are also essentially disclosed in the specification of the instant application, "it is clear that isolation of modification I is needed for the process of isolating modification II." Applicants would like to emphasize that it is improper to use the disclosure of the specification of a patent application in support of an anticipatory rejection of the claims in the same patent application. Anticipatory rejections of the claims in a patent application should be based only on the teachings of a prior art reference, not using the disclosure of the specification of the patent application to supplement the teachings of the prior art reference.

Applicants respectfully traverse the anticipatory rejection of claims 6, 9-15, 16-18, 20-28, 30, 32-35 and 45-49 over US '496 because the Examiner took a position that the properties, i.e. high purity and stability, of torsemide modification II recited in these claims would be inherent to the product of the combined method of Examples 9 and 12 since the combined method of Examples 9 and 12 of US '496 is the same method used in the instant application in preparing high purity torsemide modification II. Applicants respectfully disagree. Even if, *arguendo*, one of the Examples before Example 12 in US '496 were combined with and preceded Example 12, the combined process would not necessarily result in the products of claims 6, 9-15, 16-18, 20-

28, 30, 32-35 and 45-49 because the Example combined with Example 12 can be Example 4, 10 or 11 (which do not start with torsemide modification II), not Example 9. More importantly, as discussed above, US '496 does not disclose explicitly or implicity combining the methods of Examples 9 and 12 in a sequence. Thus, US '496 does not inherently teach the products of claims 6, 9-15, 16-18, 20-28, 30, 32-35 and 45-49.

Therefore, the anticipatory rejection of claims 1, 6, 9-18, 20-28, 30, 32-35, 39 and 43-49 over US '496 should be withdrawn.

Claim Rejections -- 35 U.S.C. 103

Applicants respectfully traverse the obviousness rejection of claims 2-5 over Dreckmann-Behrendt, by itself, or in view of Ortyl et al (US 5,738,872). The Office Action relies on the pharmaceutical composition in Example 5 of Dreckmann-Behrendt and the Office Action relies on Ortyl et al for the disclosure of pharmaceutically acceptable excipients. Applicants contend that the obviousness rejection should be withdrawn because neither Dreckmann-Behrendt nor Ortyl et al teaches or suggests including a pharmaceutically acceptable excipient in a stable pharmaceutical formulation comprising an effective amount of torsemide modification II, **wherein the excipient has a low moisture content**. Dreckmann-Behrendt, by itself, or in view of Ortyl et al, is silent on using pharmaceutical acceptable excipients of low moisture content in a pharmaceutical composition of torsemide modification II. Following the teachings of Dreckmann-Behrendt, by itself, or in view of Ortyl et al would not result in the stable pharmaceutical formulation of claims 2-5. The inclusion in the torsemide pharmaceutical formulations of pharmaceutical acceptable excipients that are anhydrous or having a lower water content than excipients used in the art as in claims 2-5 (see page 7, lines 18-19, of the instant specification) is not taught or suggested by Dreckmann-Behrendt, by itself, or in view of Ortyl et al. As a result, the obviousness rejections of claims 2-5 over Dreckmann-Behrendt, by itself, or in view of Ortyl et al, should be withdrawn.

Conclusion

If there remains any minor issues that can be resolved with a telephone interview, the Examiner is invited to call the undersigned to discuss it.

If the filing of this paper is deemed not timely, applicants petition for an appropriate extension of time. The petition fee, and any other fees that may be required in relation to this paper, can be charged to Deposit Account 11-0600, referencing Docket No. 01662/51303.

Respectfully submitted,

KENYON & KENYON LLP

Dated: June 14, 2006 By: King L. Wong

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Attachments: *The National Formulary*, United States Pharmacopeial Convention, Inc., Rockville, MD, 2003, pages 2677-2684;
The National Formulary, United States Pharmacopeial Convention, Inc., Rockville, MD, 2003, pages 2685, 2713, 2714, 2727, 2779, 2780 and 2821;
The United States Pharmacopeia, United States Pharmacopeial Convention, Inc., Rockville, MD, 2003, pages iii-xii;
The United States Pharmacopeia, United States Pharmacopeial Convention, Inc., Rockville, MD, 2003, pages 13, 1519 and 1520;
IDS and PTO-1449 Form filed on May 28, 2002.

NF 21

THE NATIONAL FORMULARY

Official from January 1, 2003

TWENTY-FIRST
EDITION

Contents

NF 21

Admissions

Articles Admitted to *NF 21* by Supplement

First Supplement (January 1, 2002)
NF MONOGRAPHS
Acacia Syrup
Diluted Acetic Acid
Anise Oil
Caraway
Caraway Oil
Cardamom Oil
Cardamom Seed
Compound Cardamom Tincture
Cherry Juice
Cherry Syrup
Chocolate
Chocolate Syrup
Clove Oil
Fennel Oil
Lemon Oil
Licorice Fluidextract
Orange Oil
Orange Syrup
Sweet Orange Peel Tincture
Vanilla
Vanilla Tincture

Second Supplement (August 1, 2002)
NF MONOGRAPHS
Carbomer Copolymer
Carbomer Interpolymer
Magnesium Aluminometasilicate
Magnesium Aluminosilicate

Revisions Appearing in *NF 21* That were Not Included in *NF 20* Including Supplements

[NOTE—The articles included in this list are noted in the book with the following symbols ▲ ▲NF21. This applies to new articles as well as sections of existing items that have been revised.]
NF MONOGRAPHS
Diluted Acetic Acid
Acetyltributyl Citrate
Acetyltriethyl Citrate
Caraway
Caraway Oil
Carboxymethylcellulose Sodium 12
Cardamom Oil
Cardamom Seed
Chamomile
Chocolate
Chondroitin Sulfate Sodium
Dextrin
Echinacea angustifolia
Powdered *Echinacea angustifolia*
Powdered *Echinacea augustifolia* Extract
Echinacea pallida
Powdered *Echinacea pallida*
Powdered *Echinacea pallida* Extract
Echinacea purpurea Root
Powdered *Echinacea purpurea*
Powdered *Echinacea purpurea* Extract
Eleuthero
Powdered Eleuthero
Powdered Eleuthero Extract
Fennel Oil
Powdered Garlic Extract
Garlic Delayed-Release Tablets
Ginkgo
American Ginseng
Powdered American Ginseng
Powdered American Ginseng Extract
Powdered Asian Ginseng
Powdered Asian Ginseng Extract
Asian Ginseng Tablets
Glucosamine Hydrochloride
Glucosamine Tablets
Glucosamine Potassium Sulfate
Glucosamine Sodium Sulfate
Goldenseal
Powdered Goldenseal
Powdered Goldenseal Extract
Hawthorn Leaf with Flower
Powdered Hawthorn Leaf with Flower
Alpha Lipoic Acid
Magnesium Aluminometasilicate
Magnesium Aluminosilicate
Milk Thistle
Powdered Milk Thistle
Powdered Milk Thistle Extract
Milk Thistle Capsules
Milk Thistle Tablets
Monoethanolamine
Poloxamer
Polyethylene Glycol
St. John's Wort
Powdered St. John's Wort
Powdered St. John's Wort Extract
Suspension Structured Vehicle
Sugar-free Suspension Structured Vehicle
Tributyl Citrate
Triethyl Citrate
Ubidecarenone
Ubidecarenone Capsules
Ubidecarenone Tablets
Valerian Tablets

Excipients

USP and NF Excipients, Listed by Categories

Acidifying Agent
Acetic Acid
Acetic Acid, Glacial
Citric Acid
Fumaric Acid
Hydrochloric Acid
Hydrochloric Acid, Diluted
Malic Acid
Nitric Acid
Phosphoric Acid
Phosphoric Acid, Diluted
Propionic Acid
Sulfuric Acid
Tartaric Acid

Aerosol Propellant
Butane
Dichlorodifluoromethane
Dichlorotetrafluoroethane
Isobutane
Propane
Trichloromonofluoromethane

Air Displacement
Carbon Dioxide
Nitrogen

Alcohol Denaturant
Denatonium Benzoate
Methyl Isobutyl Ketone
Sucrose Octaacetate

Alkalizing Agent
Ammonia Solution, Strong
Ammonium Carbonate
Diethanolamine
Potassium Hydroxide
Sodium Bicarbonate
Sodium Borate
Sodium Carbonate
Sodium Hydroxide
Trolamine

Anticaking Agent (See *Glidant*)

Antifoaming Agent
Dimethicone
Simethicone

Antimicrobial Preservative
Benzalkonium Chloride
Benzalkonium Chloride Solution
Benzethonium Chloride
Benzoic Acid
Benzyl Alcohol
Butylparaben
Cetylpyridinium Chloride
Chlorobutanol
Chlorocresol
Cresol
Ethylparaben
Methylparaben
Methylparaben Sodium
Phenol
Phenylethyl Alcohol
Phenylmercuric Acetate
Phenylmercuric Nitrate
Potassium Benzoate
Potassium Sorbate
Propylparaben
Propylparaben Sodium
Sodium Benzoate
Sodium Dehydroacetate
Sodium Propionate
Sorbic Acid
Thimerosal
Thymol

Antioxidant
Ascorbic Acid
Ascorbyl Palmitate
Butylated Hydroxyanisole
Butylated Hydroxytoluene
Hypophosphorous Acid
Monothioglycerol
Potassium Metabisulfite
Propyl Gallate
Sodium Formaldehyde Sulfoxylate
Sodium Metabisulfite
Sodium Thiosulfate
Sulfur Dioxide
Tocopherol
Tocopherols Excipient

Buffering Agent
Acetic Acid
Ammonium Carbonate
Ammonium Phosphate
Boric Acid
Citric Acid
Lactic Acid
Phosphoric Acid
Potassium Citrate
Potassium Metaphosphate
Potassium Phosphate, Monobasic
Sodium Acetate
Sodium Citrate
Sodium Lactate Solution
Sodium Phosphate, Dibasic
Sodium Phosphate, Monobasic

Bulking Agent for Freeze-Drying
Creatinine
Mannitol

Capsule Lubricant (See *Tablet and/or Capsule Lubricant*)

Chelating Agent
Edetate Calcium Disodium
Edetate Disodium
Edetic Acid

Coating Agent
Carboxymethylcellulose, Sodium
Cellacefate (formerly Cellulose Acetate Phthalate)
Cellulose Acetate
Cellulose Acetate Phthalate (see Cellacefate)
Ethylcellulose
Ethylcellulose Aqueous Dispersion
Gelatin
Glaze, Pharmaceutical
Hydroxypropyl Cellulose
Hydroxypropyl Methylcellulose

Hydroxypropyl Methylcellulose Phthalate (see Hypromellose Phthalate)
Hypromellose Phthalate (formerly Hydroxypropyl Methylcellulose Phthalate)
Methacrylic Acid Copolymer
Methacrylic Acid Copolymer Dispersion
Methylcellulose
Polyethylene Glycol
Polyvinyl Acetate Phthalate
Shellac
Sucrose
Titanium Dioxide
Wax, Carnauba
Wax, Microcrystalline
Zein

Color
Caramel
Ferric Oxide, red yellow, black, or blends

Complexing Agent
Edetate Disodium
Edetic Acid
Oxyquinoline Sulfate

Desiccant
Calcium Chloride
Calcium Sulfate
Silicon Dioxide

Emollient
Alkyl (C12-15) Benzoate

Emulsifying and/or Solubilizing Agent
Acacia
Cholesterol
Diethanolamine (Adjunct)
Glyceryl Monostearate
Lanolin Alcohols
Lecithin
Mono- and Di-glycerides
Monoethanolamine (Adjunct)
Oleic Acid (Adjunct)
Oleyl Alcohol (Stabilizer)
Poloxamer
Polyoxyethylene 50 Stearate
Polyoxyl 35 Castor Oil
Polyoxyl 40 Hydrogenated Castor Oil
Polyoxyl 10 Oleyl Ether
Polyoxyl 20 Cetostearyl Ether
Polyoxyl 40 Stearate
Polysorbate 20
Polysorbate 40
Polysorbate 60
Polysorbate 80
Propylene Glycol Monostearate
Sodium Lauryl Sulfate
Sodium Stearate
Sorbitan Monolaurate
Sorbitan Monooleate
Sorbitan Monopalmitate
Sorbitan Monostearate
Stearic Acid
Trolamine
Wax, Emulsifying

Filtering Aid
Cellulose, Powdered
Siliceous Earth, Purified

Flavors and Perfumes
Anethole
Benzaldehyde
Ethyl Vanillin
Menthol
Methyl Salicylate
Monosodium Glutamate
Peppermint
Peppermint Oil
Peppermint Spirit
Rose Oil
Rose Water, Stronger
Thymol
Vanillin

Glidant and/or Anticaking Agent
Calcium Silicate
Magnesium Silicate
Silicon Dioxide, Colloidal
Talc

Humectant
Glycerin
Hexylene Glycol
Propylene Glycol
Sorbitol

Ointment Base
Diethylene Glycol Monoethyl Ether
Lanolin
Ointment, Hydrophilic
Ointment, White
Ointment, Yellow
Polyethylene Glycol Ointment
Petrolatum
Petrolatum, Hydrophilic
Petrolatum, White
Rose Water Ointment
Squalane
Vegetable Oil, Hydrogenated, Type II

Plasticizer
Acetyltributyl Citrate
Acetyltriethyl Citrate
Castor Oil
Diacetylated Monoglycerides
Dibutyl Sebacate
Diethyl Phthalate
Glycerin
Polyethylene Glycol
Propylene Glycol
Triacetin
Tributyl Citrate
Triethyl Citrate

Polymer Membrane
Cellulose Acetate

Sequestering Agent
Beta Cyclodextrin (see Betadex)
Betadex (formerly Beta Cyclodextrin)

Solvent
Acetone
Alcohol
Alcohol, Diluted
Amylene Hydrate
Benzyl Benzoate
Butyl Alcohol
Corn Oil
Cottonseed Oil
Diethylene Glycol Monoethyl Ether
Ethyl Acetate
Glycerin
Hexylene Glycol
Isopropyl Alcohol
Methyl Alcohol
Methylene Chloride
Methyl Isobutyl Ketone
Mineral Oil
Peanut Oil
Polyethylene Glycol
Propylene Glycol
Sesame Oil
Water for Injection
Water for Injection, Sterile

Water for Irrigation, Sterile
Water, Purified

Sorbent
Cellulose, Powdered
Charcoal
Siliceous Earth, Purified

Sorbent, Carbon Dioxide
Barium Hydroxide Lime
Soda Lime

Stiffening Agent
Castor Oil, Hydrogenated
Cetostearyl Alcohol
Cetyl Alcohol
Cetyl Esters Wax
Cetyl Palmitate
Hard Fat
Paraffin
Synthetic Paraffin
Stearyl Alcohol
Wax, Emulsifying
Wax, White
Wax, Yellow

Suppository Base
Cocoa Butter
Hard Fat
Polyethylene Glycol

Suspending and/or Viscosity-increasing Agent
Acacia
Agar
Alginic Acid
Aluminum Monostearate
Attapulgite, Activated
Attapulgite, Colloidal Activated
Bentonite
Bentonite, Purified
Bentonite Magma
Carbomer 910
Carbomer 934
Carbomer 934P
Carbomer 940
Carbomer 941
Carbomer 1342
Carboxymethylcellulose Calcium
Carboxymethylcellulose Sodium
Carboxymethylcellulose Sodium 12
Carrageenan
Cellulose, Microcrystalline, and Carboxymethylcellulose Sodium
Dextrin
Gelatin
Guar Gum
Hydroxyethyl Cellulose
Hydroxypropyl Cellulose
Hydroxypropyl Methylcellulose
Magnesium Aluminum Silicate
Methylcellulose
Pectin
Polyethylene Oxide
Polyvinyl Alcohol
Povidone
Propylene Glycol Alginate
Silicon Dioxide
Silicon Dioxide, Colloidal
Sodium Alginate
Tragacanth
Xanthan Gum

Sweetening Agent
Aspartame
Dextrates
Dextrose
Dextrose Excipient
Fructose
Mannitol
Saccharin
Saccharin Calcium
Saccharin Sodium
Sorbitol
Sorbitol Solution
Sucralose
Sucrose
Sugar, Compressible
Sugar, Confectioner's
Syrup

Tablet Binder
Acacia
Alginic Acid
Carboxymethylcellulose, Sodium
Cellulose, Microcrystalline
Dextrin
Ethylcellulose
Gelatin
Glucose, Liquid
Guar Gum
Hydroxypropyl Methylcellulose
Methylcellulose
Polyethylene Oxide
Povidone
Starch, Pregelatinized
Syrup

Tablet and/or Capsule Diluent
Calcium Carbonate
Calcium Phosphate, Dibasic
Calcium Phosphate, Tribasic
Calcium Sulfate
Cellulose, Microcrystalline
Cellulose, Powdered
Dextrates
Dextrin
Dextrose Excipient
Fructose
Kaolin
Lactitol
Lactose
Mannitol
Sorbitol
Starch
Starch, Pregelatinized
Sucrose
Sugar, Compressible
Sugar, Confectioner's

Tablet Disintegrant
Alginic Acid
Cellulose, Microcrystalline
Croscarmellose Sodium
Crospovidone
Polacrilin Potassium
Sodium Starch Glycolate
Starch
Starch, Pregelatinized

Tablet and/or Capsule Lubricant
Calcium Stearate
Glyceryl Behenate
Magnesium Stearate
Mineral Oil, Light
Polyethylene Glycol
Sodium Stearyl Fumarate
Stearic Acid
Stearic Acid, Purified
Talc
Vegetable Oil, Hydrogenated, Type I
Zinc Stearate

Tonicity Agent
Dextrose
Glycerin
Mannitol

Potassium Chloride
Sodium Chloride

Vehicle

FLAVORED AND/OR SWEETENED
Aromatic Elixir
Benzaldehyde Elixir, Compound
Peppermint Water
Sorbitol Solution
Syrup
OLEAGINOUS
Alkyl (C12-15) Benzoate
Almond Oil
Corn Oil
Cottonseed Oil
Ethyl Oleate
Isopropyl Myristate
Isopropyl Palmitate
Mineral Oil
Mineral Oil, Light
Octyldodecanol
Olive Oil
Peanut Oil
Safflower Oil
Sesame Oil
Soybean Oil
Squalane
SOLID CARRIER
Sugar Spheres
STERILE
Sodium Chloride Injection, Bacteriostatic
Water for Injection, Bacteriostatic

Viscosity-Increasing (See *Suspending Agent*)

Water Repelling Agent
Cyclomethicone
Dimethicone
Simethicone

Wetting and/or Solubilizing Agent
Benzalkonium Chloride
Benzethonium Chloride
Cetylpyridinium Chloride
Docusate Sodium
Nonoxynol 9
Octoxynol 9
Poloxamer
Polyoxyl 35 Castor Oil
Polyoxyl 40 Hydrogenated Castor Oil
Polyoxyl 10 Oleyl Ether
Polyoxyl 20 Cetostearyl Ether
Polyoxyl 40 Stearate
Polysorbate 20
Polysorbate 40
Polysorbate 60
Polysorbate 80
Sodium Lauryl Sulfate
Sorbitan Monolaurate
Sorbitan Monooleate
Sorbitan Monopalmitate
Sorbitan Monostearate
Tyloxapol

General Notices and Requirements

Applying to Standards, Tests, Assays, and Other Specifications of the National Formulary

The *General Notices and Requirements* (hereinafter referred to as the *General Notices*) provide in summary form the basic guidelines for the interpretation and application of the standards, tests, assays, and other specifications of the *National Formulary* and eliminate the need to repeat throughout the book those requirements that are pertinent in numerous instances.

Where exceptions to the *General Notices* are made, the wording in the individual monograph or general test chapter takes precedence and specifically indicates the directions or the intent. To emphasize that such exceptions do exist, the *General Notices* employ where indicated a qualifying expression such as "unless otherwise specified." Thus, it is understood that the specific wording of standards, tests, assays, and other specifications is binding wherever deviations from the *General Notices* exist. By the same token, where no language is given specifically to the contrary, the *General Notices* apply.

TITLE

The full title of this publication, including its supplements, is the *National Formulary, Twenty-First Edition*. This title may be abbreviated to *NF 21*. Where the term *NF* is used, without further qualification, during the period in which this *National Formulary* is official, it refers only to *NF 21* and any supplement(s) thereto. The same titles, with no further distinction, apply equally to print or electronic presentation of these contents.

"OFFICIAL" AND "OFFICIAL ARTICLES"

The word "official," as used in this *National Formulary* or with reference hereto, is synonymous with "*National Formulary*," with "*NF*," and with "compendial."

The designation *NF* in conjunction with the official title or elsewhere on the label of an article is a reminder that the article purports to comply with *NF* standards; such specific designation on the label does not constitute a representation, endorsement, or incorporation by the manufacturer's labeling of the informational material contained in the *NF* monograph, nor does it constitute assurance by *NF* that the article is known to comply with *NF* standards. An article may only purport to comply with an *NF* standard when the article is recognized in the *NF*. The standards apply equally to articles bearing the official titles or names derived by transposition of the definitive words of official titles or transposition in the order of the names of two or more ingredients in official titles, whether or not the added designation "*NF*" is used. Names considered to be synonyms of the official titles may not be used for official titles.

Although both compendia, the United States Pharmacopeia and the National Formulary, currently are published under one cover, they remain separate compendia. The designation *USP–NF* or similar combination may be used on the label of an article, provided the label also bears a statement such as, "Meets *NF* standards as published by the USP," indicating the particular compendium to which the article purports to apply.

Where an article differs from the standards of strength, quality, and purity as determined by the application of the assays and tests, set forth for it in the *National Formulary*, its difference shall be plainly stated on its label. Where an article fails to comply in identity with the identity prescribed in the *NF*, or contains an added substance that interferes with the prescribed assays and tests, such article shall be designated by a name that is clearly distinguishing and differentiating from any name recognized in the *National Formulary*.

Articles listed herein are official, and the standards set forth in the monographs apply to them only when the articles are intended or labeled for use as drugs, as nutritional or dietary supplements, or as medical devices and when bought, sold, or dispensed for these purposes or when labeled as conforming to this *National Formulary*.

An article is deemed to be recognized in this *National Formulary* when a monograph for the article is published in it, including its supplements, addenda, or other interim revisions, and an official date is generally or specifically assigned to it.

Because of differing characteristics not standardized by this *Formulary*, all sources or types of some excipients may not have identical properties with respect to use in a specific preparation. To assure interchangeability in such instances, users may wish to ascertain final performance equivalency or determine such characteristics prior to use.

STORAGE UNDER NONSPECIFIC CONDITIONS

For articles recognized in this *National Formulary*, regardless of quantity, where no specific storage directions or limitations are provided in the individual monograph or stated in the article's labeling, it is understood that conditions of storage and distribution include protection from moisture, freezing, excessive heat, and, where necessary, protection from light.

OTHER GENERAL NOTICES

The General Notices of *USP 26*, beginning with "The following terminology is used" under "Official" and "*Official Articles*" (but not including the section *Storage under Nonspecific Conditions* under *Preservation, Packaging, Storage, and Labeling* since that topic is addressed in these *General Notices*), apply equally to the standards, test, assays, and other specifications of this *National Formulary*, the terms "National Formulary" and "NF" being read for "Pharmacopeial" and "USP," respectively.

Similarly, the *General Chapters*, the section on *Reagents, Indicators, and Solutions*, and the *Reference Tables* of *USP 26* apply also to this *National Formulary*.

Official Monographs for NF 21

Acacia

» Acacia is the dried gummy exudate from the stems and branches of *Acacia senegal* (Linné) Willdenow or of other related African species of *Acacia* (Fam. Leguminosae).

Packaging and storage—Preserve in tight containers.

Solubility and reaction—Dissolve 1 g in 2 mL of water; the resulting solution flows readily and is acid to litmus.

Botanic characteristics—

Acacia—Spheroidal tears up to 32 mm in diameter or in angular fragments of white to yellowish white color. Is translucent or somewhat opaque from the presence of numerous minute fissures; very brittle, the fractured surface glassy and occasionally iridescent. Is almost odorless and produces a mucilaginous sensation on the tongue.

Flake Acacia—White to yellowish white, thin flakes, appearing under the microscope as colorless, striated fragments.

Powdered Acacia—White to yellowish white, angular microscopic fragments with only traces of starch or vegetable tissues present.

Granular Acacia—White to pale yellowish white, fine granules. Under the microscope it appears as colorless, glassy, irregularly angular fragments up to 100 µm in thickness, some of which exhibit parallel linear streaks.

Spray-dried Acacia—White to off-white compacted microscopic fragments or whole spheres.

Identification—To 10 mL of a cold solution (1 in 50) add 0.2 mL of diluted lead subacetate TS: a flocculent, or curdy, white precipitate is formed immediately.

Microbial limits (61)—It meets the requirements of the test for absence of *Salmonella* species.

Water, *Method III* (921)—Dry it at 105° for 5 hours: it loses not more than 15.0% of its weight. For unground Acacia, crush it in a mortar until it passes through a No. 40 sieve, and mix the ground material before weighing the test specimen.

Total ash (561): not more than 4.0%.

Acid-insoluble ash (561): not more than 0.5%.

Insoluble residue—Dissolve 5.0 g of powdered or finely ground Acacia in about 100 mL of water in a 250-mL conical flask, add 10 mL of 3 N hydrochloric acid, and boil gently for 15 minutes. Filter by suction, while hot, through a tared filtering crucible, wash thoroughly with hot water, dry at 105° for 1 hour, and weigh. The weight of the residue thus obtained does not exceed 50 mg.

Arsenic, *Method II* (211): 3 ppm.

Lead (251): 0.001%.

Heavy metals, *Method II* (231): 0.004%.

Starch or dextrin—Boil a solution (1 in 50), cool, and add iodine TS: no bluish or reddish color is produced.

Organic volatile impurities, *Method I* (467): meets the requirements.

Tannin-bearing gums—To 10 mL of a solution (1 in 50) add 0.1 mL of ferric chloride TS: no blackish coloration or blackish precipitate is produced.

Acacia Syrup

» Prepare Acacia Syrup as follows (see *Pharmacy Compounding* (795)):

Acacia, granular or powdered	100 g
Sodium Benzoate	1 g
Vanilla Tincture	5 mL
Sucrose	800 g
Purified Water, a sufficient quantity to make	1000 mL

Mix Acacia, Sodium Benzoate, and Sucrose, add 425 mL of Purified Water, and mix. Heat the mixture on a steam bath until dissolved. When cool, remove the scum, add Vanilla Tincture and sufficient Purified Water to make the product measure 1000 mL, and strain, if necessary.

Packaging and storage—Preserve in tight containers, and prevent exposure to excessive heat.

Labeling—The label states the Latin binomial name and, following the official name, the part of the plant source from which the article was derived.

Microbial limits (61)—It meets the requirements of the test for absence of *Salmonella* species.

Acetic Acid

Acetic acid.
Acetic acid [64-19-7].

» Acetic Acid is a solution containing not less than 36.0 percent and not more than 37.0 percent, by weight, of $C_2H_4O_2$.

Packaging and storage—Preserve in tight containers.

Identification—It responds to the tests for *Acetate* (191).

Nonvolatile residue—Evaporate 20 mL in a tared porcelain dish on a steam bath, and dry at 105° for 1 hour: the weight of the residue does not exceed 1.0 mg (0.005%).

Chloride—Add 5 drops of silver nitrate TS to 10 mL of a solution (1 in 10): no opalescence is produced.

Sulfate—Add 5 drops of barium chloride TS to 10 mL of a solution (1 in 10): no turbidity is produced.

Heavy metals (231)—To the residue obtained in the test for *Nonvolatile residue* add 8 mL of 0.1 N hydrochloric acid, warm gently until solution is complete, dilute with water to 100 mL, and use 10 mL of the solution: the limit is 0.001%.

Phthalyl content—Transfer about 1 g, accurately weighed, to a conical flask, dissolve in 50 mL of a mixture of alcohol and acetone (3 : 2), add phenolphthalein TS, and titrate with 0.1 N sodium hydroxide VS. Perform a blank determination, and make any necessary correction. Calculate the percentage of phthalyl, on the acid-free basis, by the formula:

$$100[(1.491A/W) - 1.795B]/(100 - B),$$

in which A is the volume, in mL, of 0.1 N sodium hydroxide consumed after correction for the blank, W is the weight, in g, of Cellacefate taken, calculated on the anhydrous basis, and B is the percentage of acid found in the test for *Limit of free acid*.

Content of acetyl—Transfer about 500 mg, accurately weighed, to a glass-stoppered flask, and add 50 mL of water and 50.0 mL of 0.5 N sodium hydroxide VS. Connect the flask to a reflux condenser, and reflux for 60 minutes. Cool, add 5 drops of phenolphthalein TS, and titrate with 0.5 N hydrochloric acid VS. Perform a blank determination. Calculate the free and combined acids, as acetyl, taken by the formula:

$$2.152(A/W),$$

in which A is the volume, in mL, of 0.5 N sodium hydroxide consumed after correction for the blank, and W is the weight, in g, of Cellacefate taken, on the anhydrous basis. Calculate the percentage of acetyl, on the acid-free basis, taken by the formula:

$$[100(P - 0.5182B)/(100 - B)] - 0.5772C,$$

in which P is the free and combined acids, as acetyl, B is the percentage of acid found in the test for *Free acid*, and C is the percentage of phthalyl found in the test for *Phthalyl content*.

Microcrystalline Cellulose

Cellulose.
Cellulose [*9004-34-6*].

» Microcrystalline Cellulose is purified, partially depolymerized cellulose prepared by treating alpha cellulose, obtained as a pulp from fibrous plant material, with mineral acids.

Packaging and storage—Preserve in tight containers.

Labeling—The labeling indicates the nominal loss on drying, bulk density, and degree of polymerization values. Degree of polymerization compliance is determined using *Identification* test *C*. Where the particle size distribution is stated in the labeling, the labeling indicates the d_{10}, d_{50}, and d_{90} values and the range for each.

Identification—

A: Prepare iodinated zinc chloride solution by dissolving 20 g of zinc chloride and 6.5 g of potassium iodide in 10.5 mL of water. Add 0.5 g of iodine, and shake for 15 minutes. Place about 10 mg of Microcrystalline Cellulose on a watch glass, and disperse in 2 mL of iodinated zinc chloride solution: the substance takes on a violet-blue color.

B: Sieve 20 g for 5 minutes on an air-jet sieve equipped with a screen having 38-µm openings. If more than 5% is retained on the screen, mix 30 g of Microcrystalline Cellulose with 270 mL of water; otherwise, mix 45 g with 255 mL of water. Perform the mixing for 5 minutes in a single-speed, high-speed (equal to or greater than 18,000 rpm) power blender that has a clover-shaped jar design. The jar and blades meet the following specifications: the jar has an inside diameter of 7.0 cm at the bottom and 9.2 cm at the top and an overall height of 21.9 cm; and the 4 blades are arranged so that 2 of the blades are pointed up and 2 are pointed down. Transfer 100 mL of the dispersion to a 100-mL graduated cylinder, and allow to stand for 3 hours: a white, opaque, bubble-free dispersion, which does not form a supernatant liquid at the surface, is obtained.

C: Transfer 1.3 g of Microcrystalline Cellulose, accurately weighed to 0.1 mg, to a 125-mL conical flask. Add 25.0 mL of water and 25.0 mL of 1.0 M cupriethylenediamine hydroxide solution. Immediately purge the solution with nitrogen, insert the stopper, and shake on a wrist action shaker or other suitable mechanical shaker until completely dissolved. Transfer 7.0 mL of the solution to a calibrated number 150 Cannon-Fenske or equivalent[1] viscosimeter. Allow the solution to equilibrate at 25 ± 0.1° for not less than 5 minutes. Time the flow between the 2 marks on the viscosimeter, and record the flow time, t_1, in seconds. Calculate the kinematic viscosity, $(KV)_1$, of the Microcrystalline Cellulose taken by the formula:

$$t_1(k_1),$$

in which k_1 is the viscosimeter constant (see *Viscosity* ⟨911⟩). Obtain the flow time, t_2, for a 0.5 M cupriethylenediamine hydroxide solution using a number 100 Cannon-Fenske or equivalent[1] viscosimeter. Calculate the kinematic viscosity, $(KV)_2$, of the solvent by the formula:

$$t_2(k_2),$$

in which k_2 is the viscosimeter constant. Determine the relative viscosity, η_{rel}, of the Microcrystalline Cellulose specimen taken by the formula:

$$(KV)_1/(KV)_2.$$

Determine the intrinsic viscosity, $[\eta]c$, by interpolation, using the *Intrinsic Viscosity Table* in the *Reference Tables* section. Calculate the degree of polymerization, P, by the formula:

$$((95)[\eta]c)/(W_s[(100 - \%\,LOD)/100]),$$

in which W_s is the weight, in g, of the Microcrystalline Cellulose taken, and % *LOD* is the value obtained from the test for *Loss on drying*. The degree of polymerization is not greater than 350, and is within the labeled specification.

Microbial limits ⟨61⟩—The total aerobic microbial count does not exceed 1000 per g, the total combined molds and yeasts count does not exceed 100 per g, and it meets the requirements of the tests for absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa* and for absence of *Escherichia coli* and *Salmonella* species.

Conductivity—Shake about 5 g with 40 mL of water for 20 minutes, and centrifuge. Retain the supernatant liquid for use in the *pH* test. Using an appropriate conductivity meter that has been standardized with a potassium chloride conductivity calibration standard[2] having a conductivity of 100 µS per cm, measure the conductivity of the supernatant solution after a stable reading is obtained, and measure the conductivity of the water used to prepare the test specimen. The conductivity of the supernatant solution does not exceed the conductivity of the water by more than 75 µS per cm.

pH ⟨791⟩: between 5.0 and 7.0 in the supernatant solution obtained in the *Conductivity* test.

Loss on drying ⟨731⟩—Dry it at 105° for 3 hours: it loses not more than 7.0% of its weight, or some other lower percentage, or is within a percentage range, as specified in the labeling.

Residue on ignition ⟨281⟩: not more than 0.05%.

Bulk density—Use a volume meter[3] that has been fitted with a 10-mesh screen. The volume meter is freestanding of the brass or stainless steel cup, which is calibrated to a capacity of 25.0 ± 0.05 mL and has an inside diameter of 30.0 ± 2.0 mm. Weigh the empty cup, position it under the chute, and slowly pour the powder from a height of 5.1 cm (2 inches) above the funnel through the volume meter, at a rate suitable to prevent clogging, until the cup overflows. [NOTE—If excessive clogging of the screen occurs, remove the screen.] Level the

[1] A Ubbelohde 1C viscosimeter is equivalent to a Cannon- Fenske 150 viscosimeter. A Ubbelohde 1 viscosimeter is equivalent to a Cannon-Fenske 100 viscosimeter.

[2] Commercially available conductivity calibration solutions for conductivity meter standardization, standardized by methods traceable to the National Institute of Science and Technology (NIST), may be used. Solutions prepared according to instructions given in ASTM Standard D1125 may be used provided the conductivity of the resultant solution is the same as that of the solution prepared from the NIST-certified material.

[3] A suitable apparatus is described as the Scott Volumeter in ASTM B 329, available from the American Society for Testing and Materials, 100 Barr Harbor Drive, West Conshohocken, PA 19429-2959.

excess powder, and weigh the filled cup. Calculate the bulk density by dividing the weight of the powder in the cup by the volume of the cup: the bulk density is within the labeled specification.

Water-soluble substances—Shake 5.0 g with about 80 mL of water for 10 minutes, filter with the aid of vacuum through filter paper (Whatman No. 42 or equivalent) into a vacuum flask. Transfer the filtrate to a tared beaker, evaporate to dryness without charring, dry at 105° for 1 hour, cool in a desiccator, and weigh: the difference between the weight of the residue and the weight obtained from a blank determination does not exceed 12.0 mg (0.24%).

Ether-soluble substances—Place 10.0 g in a chromatography column having an internal diameter of about 20 mm, and pass 50 mL of peroxide-free ether through the column. Evaporate the eluate to dryness in a previously dried and tared evaporating dish with the aid of a current of air in a fume hood. After all the ether has evaporated, dry the residue at 105° for 30 minutes, cool in a desiccator, and weigh: the difference between the weight of the residue and the weight obtained from a blank determination does not exceed 5.0 mg (0.05%).

Heavy metals, *Method II* ⟨231⟩: 0.001%.

Organic volatile impurities, *Method IV* ⟨467⟩: meets the requirements.

Microcrystalline Cellulose and Carboxymethylcellulose Sodium

» Microcrystalline Cellulose and Carboxymethylcellulose Sodium is a colloid-forming, attrited mixture of Microcrystalline Cellulose and Carboxymethylcellulose Sodium. It contains not less than 75.0 percent and not more than 125.0 percent of the labeled amount of carboxymethylcellulose sodium, calculated on the dried basis. The viscosity of its aqueous dispersion of percent by weight stated on the label is not less than 60.0 percent and not more than 140.0 percent of that stated on the label in centipoises.

Packaging and storage—Preserve in tight containers, store in a dry place, and avoid exposure to excessive heat.

Labeling—Label it to indicate the percentage content of carboxymethylcellulose sodium and the viscosity of the dispersion in water of the designated weight percentage composition.

Identification—

A: Mix 6 g with 300 mL of water in a blender at 18,000 rpm for 5 minutes: a white, opaque, dispersion is produced which does not settle on standing.

B: Add several drops of the dispersion obtained in *Identification* test *A* to a solution of aluminum chloride (1 in 10): each drop forms a white, opaque globule which does not disperse on standing.

C: Add 3 mL of iodine TS to the dispersion obtained in *Identification* test *A*: no blue or purplish blue color is produced.

Viscosity ⟨911⟩—Determine the amounts of Microcrystalline Cellulose and Carboxymethylcellulose Sodium needed to prepare 600 g of a suitable dispersion, calculated on the dried basis. Transfer an accurately weighed amount of water to a 1000-mL blender-bowl. Begin stirring with an 18,000 rpm blender at a reduced speed obtained by adjusting the voltage to 30 volts by means of a suitable transformer, and immediately add the accurately weighed portion of Microcrystalline Cellulose and Carboxymethylcellulose Sodium, taking care to avoid contacting the sides of the bowl with the powder. Continue stirring at this speed for 15 seconds following the addition of the powder, then increase the transformer setting to 115 volts, and mix for 2 minutes, accurately timed, at 18,000 rpm. Stop the blender, and lower the appropriate spindle of a suitable rotational viscosimeter into the dispersion. Thirty seconds after cessation of mixing, start the viscosimeter, and determine the viscosity using the appropriate spindle to obtain a scale reading between 10% and 90% of full-scale at a speed of 20 rpm. Determine the scale reading after 30 seconds of rotation, and calculate the viscosity, in centipoises, by multiplying the scale reading by the constant for the spindle used at 20 rpm.

pH ⟨791⟩: between 6.0 and 8.0, determined on the dispersion prepared in the test for *Viscosity*.

Loss on drying ⟨731⟩—Dry it at 105° to constant weight: it loses not more than 8.0% of its weight.

Residue on ignition ⟨281⟩: not more than 5.0%.

Heavy metals, *Method II* ⟨231⟩: 0.001%.

Organic volatile impurities, *Method IV* ⟨467⟩: meets the requirements.

Assay for carboxymethylcellulose sodium—Transfer about 2 g of Microcrystalline Cellulose and Carboxymethylcellulose Sodium, accurately weighed, to a glass-stoppered, 250-mL conical flask. Add 75 mL of glacial acetic acid, attach a condenser, and reflux for 2 hours. Cool, transfer the mixture to a 250-mL beaker with the aid of small volumes of glacial acetic acid, and titrate with 0.1 N perchloric acid in dioxane VS, determining the endpoint potentiometrically. Each mL of 0.1 N perchloric acid is equivalent to 29.6 mg of carboxymethylcellulose sodium.

Cellulose, Oxidized—*see Cellulose, Oxidized USP*

Cellulose, Oxidized Regenerated—*see Cellulose, Oxidized Regenerated USP*

Powdered Cellulose

» Powdered Cellulose is purified, mechanically disintegrated cellulose prepared by processing alpha cellulose obtained as a pulp from fibrous plant materials.

Packaging and storage—Preserve in tight containers.

Labeling—The labeling indicates the nominal degree of polymerization value. Degree of polymerization compliance is determined using *Identification* test *C*.

Identification—

A: Prepare iodinated zinc chloride solution by dissolving 20 g of zinc chloride and 6.5 g of potassium iodide in 10.5 mL of water. Add 0.5 g of iodine, and shake for 15 minutes. Place about 10 mg of Powdered Cellulose on watch glass, and disperse in 2 mL of iodinated zinc chloride solution: the substance takes on a violet-blue color.

B: Mix 30 g with 270 mL of water in a single-speed, high-speed (equal to or greater than 18,000 rpm) power blender that has a clover-shaped jar design for 5 minutes. The jar and blades meet the following specifications: the jar has an inside diameter of 7.0 cm at the bottom and 9.2 cm at the top, and an overall height of 21.9 cm; and the 4 blades are arranged so that 2 of the blades are pointed up and 2 are pointed down. Transfer 100 mL of the dispersion to a 100-mL graduated cylinder, and allow to stand for 1 hour: the Powdered Cellulose settles in the cylinder, and a supernatant liquid appears above the layer of the cellulose.

C: Transfer 0.25 g of Powdered Cellulose, accurately weighed to 0.1 mg, to a 125-mL conical flask. Proceed as directed for *Identification* test *C* under *Microcrystalline Cellulose*, beginning with "Add 25.0 mL of water." The degree of polymerization is between 440 and 2250 and is within the labeled specification.

Microbial limits ⟨61⟩—The total aerobic microbial count does not exceed 1000 per g, the total combined molds and yeasts count does not exceed 100 per g, and it meets the requirements of the tests for absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa* and for absence of *Escherichia coli* and *Salmonella* species.

pH ⟨791⟩—Mix 10 g with 90 mL of water, and allow to stand with occasional stirring for 1 hour: the pH of the supernatant liquid is between 5.0 and 7.5.

basis as directed under *Residue on Ignition* ⟨281⟩, using sufficient sulfuric acid to moisten the entire residue after the initial charring step, and additional sulfuric acid if an excessive amount of carbonaceous material remains after the initial complete volatilization of white fumes.

Calculate the degree of acid carboxymethyl substitution, *A*, taken by the formula:

$$1150M/(7102 - 412M - 80C).$$

Calculate the degree of sodium carboxymethyl substitution, *S*, taken by the formula:

$$(162 + 58A)C/(7102 - 80C).$$

The degree of substitution is the sum of $A + S$. It is between 0.60 and 0.85, calculated on the dried basis.

Content of water-soluble material—Disperse about 10 g, accurately weighed, in 800 mL of water, accurately measured, and stir for 1 minute every 10 minutes during the first 30 minutes. Allow to stand for an additional hour, or centrifuge, if necessary. Decant about 200 mL of the aqueous slurry onto a rapid-filtering filter paper in a vacuum filtration funnel, apply vacuum, and collect about 150 mL of the filtrate. Pour the filtrate into a tared 250-mL beaker, weigh accurately, and calculate the weight, in g, of the filtrate, W_1, by difference. Concentrate on a hot plate to a small volume, but not to dryness, dry at 105° for 4 hours, again weigh, and calculate the weight, in g, of residue W_3, by difference. Calculate the percentage of water-soluble material in the specimen, on the dried basis, taken by the formula:

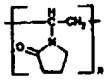
$$100W_1(800 + W_2)/[W_2W_3(1 - 0.01b)],$$

in which W_2 is the weight, in g, of the specimen taken, and b is the percentage *Loss on drying* of the specimen taken. It is between 1.0% and 10.0%.

Settling volume—To 75 mL of water in a 100-mL graduated cylinder add 1.5 g of it in 0.5-g portions, shaking vigorously after each addition. Add water to make 100 mL, shake again until all of the powder is homogeneously distributed, and allow to stand for 4 hours. Note the volume of the settled mass. It is between 10.0 and 30.0 mL.

Organic volatile impurities, *Method IV* ⟨467⟩: meets the requirements.

Crospovidone



$(C_6H_9NO)_n$
1-Ethenyl-2-pyrrolidinone homopolymer.
1-Vinyl-2-pyrrolidinone homopolymer [*9003-39-8*].

» Crospovidone is a water-insoluble synthetic cross-linked homopolymer of *N*-vinyl-2-pyrrolidinone. It contains not less than 11.0 percent and not more than 12.8 percent of nitrogen (N), calculated on the anhydrous basis.

Packaging and storage—Preserve in tight containers.

USP Reference standards ⟨11⟩—*USP Crospovidone RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩, on specimen previously dried in vacuum at 105° for 1 hour.

B: Suspend 1 g in 10 mL of water, add 0.1 mL of 0.1 N iodine, and shake for 30 seconds. Add 1 mL of starch TS, and shake: no blue color develops.

pH ⟨791⟩: between 5.0 and 8.0, in an aqueous suspension (1 in 100).

Water, *Method I* ⟨921⟩: not more than 5.0%.

Residue on ignition ⟨281⟩: not more than 0.4%, a 2-g specimen being used.

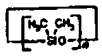
Water-soluble substances—Transfer 25.0 g of Crospovidone to a 400-mL beaker, add 200 mL of water, and stir on a magnetic stirrer, using a 5-cm stirring bar, for 1 hour. Transfer to a 250-mL volumetric flask with the aid of about 25 mL of water, add water to volume, and mix. Allow the bulk of the solids to settle. Pass about 100 mL of the relatively clear supernatant through a membrane filter having a 0.45-µm porosity, protected against clogging by superimposing a membrane filter having a 3-µm porosity. While filtering, stir the solution above the filter manually or with a mechanical stirrer, taking care not to physically damage the membrane filter. Transfer 50.0 mL of the clear filtrate to a tared 100-mL beaker, evaporate to dryness, and dry at 110° for 3 hours: the weight of the residue does not exceed 75 mg (1.50%).

Heavy metals, *Method II* ⟨231⟩: 0.001%.

Vinylpyrrolidinone—Suspend 4.0 g in 30 mL of water, stir for 15 minutes, centrifuge the suspension, and filter the slightly turbid upper layer through a sintered-glass, 10-µm filter. Stir the lower layer with 50 mL of water, centrifuge, and filter the upper layer through the same filter. Again stir the lower layer with 50 mL of water, and filter similarly. Add 0.5 g of sodium acetate to the combined filtrates, and titrate with 0.1 N iodine VS until the color of iodine no longer fades. Add 3.0 mL of 0.1 N iodine VS, allow to stand for 10 minutes, and titrate the excess iodine with 0.1 N sodium thiosulfate VS, adding 3 mL of starch TS as the endpoint is approached. Perform a blank determination (see *Residual Titrations* under *Titrimetry* ⟨541⟩), using the same total volume of the same 0.1 N iodine VS, accurately measured, as was used for titrating the specimen. Before titrating the blank, adjust with acetic acid to the same pH as that of the specimen: not more than 0.72 mL of 0.1 N iodine is consumed, corresponding to not more than 0.1% of vinylpyrrolidinone.

Nitrogen content—Proceed as directed under *Nitrogen Determination, Method II* ⟨461⟩, using about 0.1 g, accurately weighed, of Crospovidone. In the procedure, omit the use of hydrogen peroxide, and use 5 g of a powdered mixture of potassium sulfate, cupric sulfate, and titanium dioxide (33 : 1 : 1), instead of potassium sulfate and cupric sulfate (10 : 1). Heat until a clear, light green solution is obtained, and heat for an additional 45 minutes; and proceed as directed for *Procedure*, beginning with "Cautiously add to the digestion mixture 70 mL of water."

Cyclomethicone



$(C_2H_6OSi)_n$
Cyclopolydimethylsiloxane.
Cyclomethicone [*69430-24-6*].

» Cyclomethicone is a fully methylated cyclic siloxane containing repeating units of the formula:

$$[-(CH_3)_2SiO-]_n$$

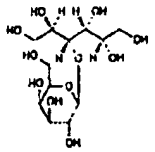
in which n is 4, 5, or 6, or a mixture of them. It contains not less than 98.0 percent of $(C_2H_6OSi)_n$, calculated as the sum of cyclomethicone 4, cyclomethicone 5, and cyclomethicone 6, and not less than 95.0 percent and not more than 105.0 percent of the labeled amount of any one or more of the individual cyclomethicone components.

Packaging and storage—Preserve in tight containers.

Labeling—Label it to state, as part of the official title, the *n*-value of the Cyclomethicone. Where it is a mixture of 2 or 3 such cyclic siloxanes, the label states the *n*-value and percentage of each in the mixture.

USP Reference standards ⟨11⟩— *USP Cyclomethicone 4 RS. USP Cyclomethicone 5 RS. USP Cyclomethicone 6 RS.*

Lactitol



$C_{12}H_{24}O_{11}$. 344.31
4-*O*-β-D-Galactopyranosyl-D-glucitol [*585-86-4*].
Monohydrate. 362.34 [*81025-04-9*].
Dihydrate. 380.35 [*81025-03-8*].

» Lactitol contains not less than 98.0 percent and not more than 101.0 percent of $C_{12}H_{24}O_{11}$, calculated on the anhydrous basis.

Packaging and storage—Preserve in well-closed containers.

Labeling—Label it to indicate whether it is the monohydrate, the dihydrate, or the anhydrous form.

USP Reference standards ⟨11⟩—*USP Lactitol RS.*

Identification—*Infrared Absorption* ⟨197K⟩.

Water, *Method I* ⟨921⟩—between 4.5% and 5.5% (monohydrate); between 9.5% and 10.5% (dihydrate); and not more than 0.5% for the anhydrous form.

Residue on ignition ⟨281⟩: not more than 0.5%.

Heavy metals ⟨231⟩—Dissolve 4 g of it in 25 mL of water: the limit is 5 µg per g.

Reducing sugars—Dissolve 500 mg of it in 2.0 mL of water in a 10-mL conical flask. Into a similar flask, pipet 2 mL of a dextrose solution containing 0.5 mg per mL. Concomitantly add 1 mL of alkaline cupric tartrate TS to each solution, heat to boiling, and cool: the lactitol solution shows no more turbidity than that produced in the dextrose solution, in which a reddish brown precipitate forms (0.2%, as dextrose).

Organic volatile impurities, *Method IV* ⟨467⟩: meets the requirements.

Related compounds—

Chromatographic system—Proceed as directed in the *Assay*, except to chromatograph the *Standard solution* instead of the *Standard preparation*.

Standard solution—Dissolve an accurately weighed quantity of USP Lactitol RS in water to obtain a solution having a known concentration of about 0.3 mg per mL.

Test solution—Use the *Assay preparation*, prepared as directed in the *Assay*.

Procedure—Separately inject equal volumes (about 25 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. The relative retention times are about 0.53 for lactose, 0.58 for glucose, 0.67 for galactose, 0.72 for lactulitol, 1.0 for lactitol, 1.55 for galactitol, and 1.68 for sorbitol. Calculate the percentages of galactitol, sorbitol, lactulitol, lactose, glucose, and galactose in the portion of Lactitol taken by the formula:

$$1000(C/W)(r_U/r_S),$$

in which C is the concentration, in mg per mL, of USP Lactitol RS in the *Standard solution*, W is the weight, in mg, of Lactitol in the *Test solution*, r_U is the peak response of the relevant related compound, if observed, obtained from the *Test solution*, and r_S is the lactitol peak response obtained from the *Standard solution*. The total of the percentages of all related compounds is not more than 1.5%.

Assay—

Mobile phase—Use water.

Standard preparation—Dissolve an accurately weighed quantity of USP Lactitol RS in water to obtain a solution having a known concentration of about 10.0 mg per mL.

Assay preparation—Transfer about 1000 mg of Lactitol, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with water to volume, and mix.

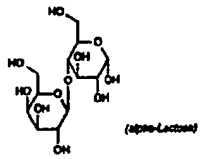
Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a refractive index detector and a 7.8-mm × 30-cm column that contains packing L34. The column is maintained at 85°, and the flow rate is about 0.7 mL per minute. Chromatograph the *Standard preparation*, and record the peak responses as directed under *Procedure:* the relative standard deviation for replicate injections is not more than 1.0% for lactitol.

Procedure—Separately inject equal volumes (about 25 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the quantity, in mg, of $C_{12}H_{24}O_{11}$ in the portion of Lactitol taken by the formula:

$$100C(r_U/r_S),$$

in which C is the concentration, in mg per mL, of USP Lactitol RS in the *Standard preparation*, and r_U and r_S are the lactitol peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively.

Anhydrous Lactose



» Anhydrous Lactose is primarily beta lactose or a mixture of alpha and beta lactose.

Labeling—Where the labeling indicates the relative quantities of alpha and beta lactose, determine compliance using *Content of alpha and beta anomers*.

USP Reference standards ⟨11⟩—*USP Anhydrous Lactose RS. USP Sucrose RS. USP Fructose RS. USP Dextrose RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: Proceed as directed in *Identification* test *B* under *Lactose Monohydrate*, except to use USP Anhydrous Lactose RS instead of USP Lactose Monohydrate RS in *Standard solution A* and *B* and to use Anhydrous Lactose in the *Test solution*.

C: Proceed as directed in *Identification* test *C* under Lactose Monohydrate.

Loss on drying ⟨731⟩—Dry it at 80° for 2 hours: it loses not more than 0.5% of its weight.

Water, *Method I* ⟨921⟩: not more than 1.0%, determined on a preparation containing anhydrous lactose in a mixture of methanol and formamide (2:1).

Heavy metals, *Method II* ⟨231⟩: 5 µg per g.

Content of alpha and beta anomers—

Silylation reagent—Prepare a mixture of pyridine and trimethylsilylimidazole (72:28).

Resolution mixture—Prepare a mixture of alpha lactose monohydrate and beta lactose having an anomeric ratio of about 1:1 based on the labeled anomeric contents of the alpha lactose monohydrate and the beta lactose.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and a 0.9-m × 4-mm glass column packed with 3% liquid phase G19 on support S1A. The column is maintained at about 215°, and the injection port and the detector are maintained at about 275°. The carrier gas is helium, flowing at a rate of about 40 mL per minute.

Derivatization procedure—Transfer about 1 mg of Anhydrous Lactose to a 5-mL reaction vial equipped with a screw cap, add 0.45 mL of dimethyl sulfoxide, seal the vial tightly with a screw cap, and mix on a vortex mixer to dissolve. Add 1.8 mL of *Silylation*

reagent, seal the vial tightly with a screw cap, and mix gently. Transfer about 1 mg of *Resolution mixture* to a second 5-mL reaction vial equipped with a screw cap, add 0.45 mL of dimethyl sulfoxide, seal the vial tightly with a screw cap, and mix on a vortex mixer to dissolve. Add 1.8 mL of *Silylation reagent*, seal the vial tightly with a screw cap, and mix gently. Maintain both vials at room temperature for 20 minutes before using.

Procedure—Inject a 2.0-µL portion of the derivatized *Resolution mixture* into the chromatograph, and record the peak areas for the major peaks: the relative retention times are about 0.7 for the silyl derivative of alpha lactose and 1.0 for the silyl derivative of beta lactose, and the resolution, R, between the two peaks is not less than 3.0. Similarly inject a 2.0-µL portion of the derivatized Anhydrous Lactose into the chromatograph, and record the peak areas for the major peaks. Determine the percentage of alpha anomer in the Anhydrous Lactose by the formula:

$$100r_a/(r_a + r_b),$$

in which r_a is the response of the alpha anomer silyl derivative peak and r_b is the response of the beta anomer silyl derivative peak. Determine the percentage of beta anomer in the Anhydrous Lactose by the formula:

$$100r_b/(r_a + r_b).$$

Other requirements—It meets the requirements for *Packaging and storage*, *Labeling*, *Clarity and color of solution*, *Specific rotation* ⟨781⟩, *Microbial limits* ⟨61⟩, *Acidity or alkalinity*, *Residue on ignition* ⟨281⟩, and *Protein and light-absorbing impurities* under *Lactose Monohydrate*.

Lactose Monohydrate

» Lactose Monohydrate is a natural disaccharide, obtained from milk, which consists of one glucose and one galactose moiety. [NOTE—Lactose Monohydrate may be modified as to its physical characteristics. It may contain varying proportions of amorphous lactose.]

Packaging and storage—Preserve in tight containers.

Labeling—Where the labeling states the particle size distribution, it also indicates the d_{10}, d_{50}, and d_{90} values and the range for each. For modified Lactose Monohydrate, also label it to indicate the method of modification.

USP Reference standards ⟨11⟩—*USP Lactose Monohydrate RS*. *USP Sucrose RS*. *USP Fructose RS*. *USP Dextrose RS*.

Clarity and color of solution—A solution of 1 g in 10 mL of boiling water is clear and nearly colorless. Determine the absorbance of this solution at a wavelength of 400 nm. The absorbance divided by the path length in centimeters is not more than 0.04.

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: *Diluent*—Prepare a mixture of methanol and water (3:2).

Developing solvent—Prepare a solution consisting of a mixture of ethylene dichloride, glacial acetic acid, methanol, and water (50:25:15:10).

Standard solution A—Prepare a solution of USP Lactose Monohydrate RS in *Diluent* having a known concentration of 0.5 mg per mL.

Standard solution B—Prepare a solution of USP Dextrose RS, USP Lactose Monohydrate RS, USP Fructose RS, and USP Sucrose RS in *Diluent* having a known concentration of 0.5 mg per mL for each Reference Standard.

Test solution—Transfer about 25 mg of Lactose Monohydrate to a 50-mL volumetric flask, dissolve in and dilute with *Diluent* to volume, and mix.

Procedure—Apply separately 2 µL each of *Standard solution A*, *Standard solution B*, and the *Test solution* to a thin-layer chromatographic plate (see *Chromatography* ⟨621⟩) coated with a 0.25-mm layer of chromatographic silica gel. Allow the spots to dry, and develop the plate in a paper-lined chromatographic chamber equilibrated with *Developing solvent* for about 1 hour prior to use. Allow the chromatogram to develop until the solvent front has moved about three-quarters of the length of the plate. Remove the plate from the chamber, dry in a current of warm air, and redevelop the plate in fresh *Developing solvent*. Remove the plate from the chamber, mark the solvent front, and dry the plate in a current of warm air. Spray the plate evenly with a solution containing 0.5 g of thymol in a mixture of 95 mL of alcohol and 5 mL of sulfuric acid. Heat the plate at 130° for 10 minutes: the principal spot obtained from the *Test solution* corresponds in appearance and R_f value to that obtained from *Standard solution A*. The test is not valid unless the chromatogram obtained with *Standard solution B* shows four clearly discernible spots, disregarding any spots at the origin.

C: Dissolve 250 mg in 5 mL of water. Add 3 mL of ammonium hydroxide, and heat in a water bath at 80° for 10 minutes: a red color develops.

Specific rotation ⟨781⟩—Dissolve 10 g by heating in 80 mL of water to 50°. Allow to cool, and add 0.2 mL of 6 N ammonium hydroxide. Allow to stand for 30 minutes, and dilute with water to 100 mL: the specific rotation, calculated on the anhydrous basis, determined at 20°, is between +54.4° and +55.9°.

Microbial limits ⟨61⟩—The total aerobic microbial count does not exceed 100 per g, the total combined molds and yeasts count does not exceed 50 per g, and it meets the requirements of the test for absence of *Escherichia coli*.

Acidity or alkalinity—Dissolve 6 g by heating in 25 mL of carbon dioxide-free water, cool, and add 0.3 mL of phenolphthalein TS: the solution is colorless, and not more than 0.4 mL of 0.1 N sodium hydroxide is required to produce a red color.

Loss on drying ⟨731⟩—Dry it at 80° for 2 hours: the monohydrate form loses not more than 0.5% of its weight, and the modified monohydrate form loses not more than 1.0% of its weight.

Water, *Method I* ⟨921⟩: between 4.5% and 5.5%, determined on a preparation containing lactose monohydrate in a mixture of methanol and formamide (2:1).

Residue on ignition ⟨281⟩: not more than 0.1%, determined on a specimen ignited at a temperature of 600 ± 25°.

Heavy metals ⟨231⟩—Dissolve 4 g in 20 mL of warm water, add 1 mL of 0.1 N hydrochloric acid, and dilute with water to 25 mL: the limit is 5 µg per g.

Protein and light-absorbing impurities ⟨851⟩—Measure the light absorption of a 1% (w/v) solution in the range of 210 to 300 nm. The absorbance divided by the path length in centimeters is not more than 0.25 in the range of 210 to 220 nm and is not more than 0.07 in the range of 270 to 300 nm.

Lanolin, Modified—*see Lanolin, Modified USP*

Lanolin Alcohols

» Lanolin Alcohols is a mixture of aliphatic alcohols, triterpenoid alcohols, and sterols, obtained by the hydrolysis of Lanolin. It may contain not more than 0.1 percent of a suitable antioxidant.

Packaging and storage—Preserve in well-closed, light-resistant containers, preferably at controlled room temperature.

Identification—Dissolve 0.5 g in 5 mL of chloroform, and add 1 mL of acetic anhydride and 2 drops of sulfuric acid: a green color is produced.

Melting range, *Class II* ⟨741⟩: not below 56°.

Acidity and alkalinity—Boil 10 g with 100 mL of water for 5 minutes, with frequent stirring. Remove the source of heat, add 0.5 mL of phenolphthalein TS, and stir: no pink color is produced. Add 0.5 mL of methyl orange TS, and stir: no red color is produced.

Loss on drying ⟨731⟩—Dry it at 105° for 1 hour: it loses not more than 0.5% of its weight.

Residue on ignition ⟨281⟩: not more than 0.15%.

the same volume, accurately measured, to the control, and mix. Then add to the control sodium fluoride TS (10 µg of F per mL) from a buret to make the colors of the two tubes match after dilution to the same volume. Mix, and allow all air bubbles to escape before making the final color comparison. Check the endpoint by adding 1 or 2 drops of sodium fluoride TS to the control. A distinct change in color appears. The volume of sodium fluoride TS required for the control solution does not exceed 1.0 mL (0.001%).

Assay—Mix about 200 mg of Potassium Metaphosphate, accurately weighed, with 15 mL of nitric acid and 30 mL of water, boil for 30 minutes, cool, and dilute with water to about 100 mL. Heat to 60°, add an excess of ammonium molybdate TS, and heat at 50° for 30 minutes. Filter, and wash the precipitate, first with 0.5 N nitric acid, and then potassium nitrate solution (1 in 100) until the filtrate is no longer acid to litmus. Add 25 mL of water to the precipitate, dissolve it in 50.0 mL of 1 N sodium hydroxide VS, add phenolphthalein TS, and titrate the excess sodium hydroxide with 1 N sulfuric acid VS. Each mL of 1 N sodium hydroxide is equivalent to 3.086 mg of P_2O_5.

Monobasic Potassium Phosphate

KH_2PO_4 136.09
Phosphoric acid, monopotassium salt.
Monopotassium phosphate [*7778-77-0*].

» Monobasic Potassium Phosphate, dried at 105° for 4 hours, contains not less than 98.0 percent and not more than 100.5 percent of KH_2PO_4.

Packaging and storage—Preserve in tight containers.

Identification—A solution (1 in 20) responds to the tests for *Potassium* ⟨191⟩ and for *Phosphate* ⟨191⟩.

Loss on drying ⟨731⟩—Dry it at 105° for 4 hours: it loses not more than 1.0% of its weight.

Insoluble substances—Dissolve 10 g in 100 mL of hot water, filter through a tared filtering crucible, wash the insoluble residue with hot water, and dry at 105° for 2 hours: the residue does not exceed 20 mg (0.2%).

Arsenic, *Method I* ⟨211⟩: 3 ppm.

Lead—A solution of 1 g in 20 mL of water contains not more than 5 µg of lead (corresponding to not more than 5 ppm of Pb) when tested as directed in the test for *Lead* ⟨251⟩.

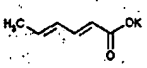
Heavy metals, *Method I* ⟨231⟩—Dissolve 1 g in 25 mL of water: the limit is 0.002%.

Limit of fluoride—Proceed as directed in the test for *Fluoride* under *Dibasic Calcium Phosphate*. The limit is 0.001%.

Organic volatile impurities, *Method I* ⟨467⟩: meets the requirements.

Assay—Transfer about 5 g of Monobasic Potassium Phosphate, previously dried and accurately weighed, to a 250-mL beaker, add 100 mL of water and 5.0 mL of 1 N hydrochloric acid VS, and stir until the assay specimen is completely dissolved. Place the electrodes of a suitable pH meter in the solution, and slowly titrate the excess acid, stirring constantly, with 1 N sodium hydroxide VS to the inflection point occurring at about pH 4. Record the buret reading, and calculate the volume (*A*), if any, of 1 N hydrochloric acid consumed by the assay specimen. Continue the titration with 1 N sodium hydroxide VS until the inflection point occurring at about pH 8.8 is reached, record the buret reading, and calculate the volume (*B*) of 1 N sodium hydroxide required in the titration between the two inflection points (pH 4 and 8.8). Each mL of the volume (*B* − *A*) of 1 N sodium hydroxide is equivalent to 136.1 mg of KH_2PO_4.

Potassium Sorbate



$C_6H_7KO_2$ 150.22
2,4-Hexadienoic acid, (*E,E*)-, potassium salt; 2,4-Hexadienoic acid, potassium salt.
Potassium (*E,E*)-sorbate; Potassium sorbate [*590-00-1; 24634-61-5*].

» Potassium Sorbate contains not less than 98.0 percent and not more than 101.0 percent of $C_6H_7KO_2$, calculated on the dried basis.

Packaging and storage—Preserve in tight containers, protected from light, and avoid exposure to excessive heat.

Identification—

A: Dissolve 1 g in 10 mL of water: the solution responds to the test for *Potassium* ⟨191⟩.

B: Dissolve 0.2 g in 2 mL of water, and add a few drops of bromine TS: the color is discharged.

Acidity or alkalinity—Dissolve 1.1 g in 20 mL of water, and add phenolphthalein TS. If the solution is colorless, titrate with 0.10 N sodium hydroxide to a pink color that persists for 15 seconds: not more than 1.1 mL is required. If the solution is pink in color, titrate with 0.10 N hydrochloric acid: not more than 0.80 mL is required to discharge the pink color.

Loss on drying ⟨731⟩—Dry it at 105° for 3 hours: it loses not more than 1.0% of its weight.

Heavy metals, *Method II* ⟨231⟩: 0.001%.

Organic volatile impurities, *Method I* ⟨467⟩: meets the requirements.

Assay—Dissolve about 300 mg of Potassium Sorbate, accurately weighed, in 40 mL of glacial acetic acid, warming, if necessary, to effect solution. Cool to room temperature, add 1 drop of crystal violet TS, and titrate with 0.1 N perchloric acid VS to a blue-green endpoint. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 15.02 mg of $C_6H_7KO_2$.

Povidone—*see Povidone USP*

Propane

C_3H_8 44.10
[*74-98-6*].

» Propane contains not less than 98.0 percent of C_3H_8.
Caution—Propane is highly flammable and explosive.

Packaging and storage—Preserve in tight cylinders, and prevent exposure to excessive heat.

Identification—

A: The IR absorption spectrum of it exhibits maxima, among others, at about the following wavelengths, in µm: 3.4 (*vs*), 6.8 (*s*), and 7.2 (*m*).

B: The vapor pressure of a test specimen, obtained as directed in the *General Sampling Procedure* under *Propellants* (see *Aerosols, Metered-Dose Inhalers, and Dry Powder Inhalers* ⟨601⟩), determined at 21° by means of a suitable pressure gauge, is between 820 and 875 kPa absolute (119 and 127 psia).

Water: not more than 0.001%, determined as directed for *Water Content* under *Aerosols, Metered-Dose Inhalers, and Dry Powder Inhalers* ⟨601⟩.

2003

USP 26

THE UNITED STATES PHARMACOPEIA

NF 21

THE NATIONAL FORMULARY

By authority of the United States Pharmacopeial Convention, Inc., meeting at Washington, D.C., April 12–16, 2000. Prepared by the Council of Experts and published by the Board of Trustees

Official from January 1, 2003

The designation on the cover of this publication, "USP NF 2003," is for ease of identification only. The publication contains two separate compendia: The Pharmacopeia of the United States Twenty-sixth Revision, and the National Formulary, Twenty-first Edition.

UNITED STATES PHARMACOPEIAL CONVENTION, INC.
12601 Twinbrook Parkway, Rockville, MD 20852

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MISSION STATEMENT

Promoting the Public Health

USP–NF is published in continuing pursuit of USP's mission, which is:

> "to promote the public health and benefit practitioners and patients by disseminating authoritative standards and information developed by its volunteers for medicines, other health care technologies, and related practices used to maintain and improve health and promote optimal health care delivery."

Working with many constituencies and stakeholders around the world, USP's compendial activities support the availability of safe, good quality medicines for consumers everywhere.

PREFACE

This preface provides general information about the 26th revision of the *United States Pharmacopeia* (*USP 26*) and the 21st edition of the *National Formulary* (*NF 21*). Additional official information about the specific uses of these texts is provided in the *General Notices and Requirements* (page 1).

History—Practitioners created the early *USP* to provide a list of the best therapeutic products, give them useful names, and indicate recipes for their preparation. On December 15, 1820, the first edition of *USP*—essentially a "recipe book" for 217 drugs and drug preparations—was published. Starting in 1880, the nature of the Pharmacopeia changed from a text containing recipes to one containing product standards. From 1820 to 1942 USP published the *Pharmacopeia* at 10-year intervals, from 1942 to 2000 at 5-year intervals, and beginning in 2002, annually. In 1888, the American Pharmaceutical Association published the first national formulary under the title *The National Formulary of Unofficial Preparations*. The title was changed to the *National Formulary* in response to the United States Food and Drugs Act of 1906, when both the *USP* and *NF* standards were referenced. In 1975, USP acquired the *NF* and began publishing this compendium concurrently with *USP* in a single volume titled *USP–NF*. This approach eliminates duplicative text and permits a single index.

Rules and Procedures—*USP–NF* standards are recognized widely because they are authoritative and science-based and are established through a transparent and credible process with established integrity. USP is incorporated as a nonprofit corporation in the District of Columbia. The organization's Articles of Incorporation, Constitution and Bylaws, and Rules and Procedures appear in Appendices A, B, and C. USP's conflict of interest policy requires all members of the Council of Experts, its Expert Committees and their ad hoc advisory panels, Board of Trustees, and staff to disclose financial interests in companies that are subject to USP standards or that may be influenced by USP information (Appendix D). USP's conflict of interest policy ensures not only the credibility of the revision process but also brings accountability to the overall process. All members of USP's governing and standards-setting bodies are unpaid volunteers. The USP Document Disclosure Policy (Appendix E) contributes to the transparency of the standards-setting process yet provides protection to manufacturers and others in submitting confidential information. Authoritative standards are recognized as representing "scientific truth" at the time they are established and can be relied upon by their users. As science and technology evolve, so do *USP* and *NF*, which undergo continuous revision.

Publications

USP 26–NF 21—USP 26–NF 21 text is official as of January 1, 2003, unless otherwise noted. *USP–NF* contains official substance and preparation (product) monographs. An official substance is defined as an active or inactive ingredient, a nutrient, a dietary supplement ingredient, and/or a pharmaceutical ingredient or a component of an official device. An official preparation refers to the finished dosage form, device, or dietary supplement product. Because *USP–NF* contains practitioner-based standards for all therapeutic products, as presented by decisions of the Council of Experts, *USP* monographs are also useful to compounding practitioners. The monograph for an official article includes its name, definition, description, packaging, storage and other requirements, and a specification. The specification consists of a series of tests, one or more analytical procedures for the test, and acceptance criteria. Ingredients are defined as either active ingredients or excipients. An excipient is any component, other than the active substance(s), intentionally added to the formulation of a dosage form. It is not necessarily inert. *USP 26–NF 21* contains approximately 4000 monographs and over 160 *General Tests* and *Assays* (⟨1000⟩ and below) and *General Information* (above ⟨1000⟩) *Chapters*. *General Chapters* provide frequently cited procedures, sometimes with acceptance criteria, to conserve text. Compared to *USP 25–NF 20*, *USP 26–NF 21* contains 128 new monographs, 357 revised monographs, and 5 new *General Chapters*. Obsolete matter deleted from this edition is indicated on page liii in the Admissions section.

Organization of the Compendia—Monographs for active ingredients and preparations appear in *USP*. Monographs for dietary and nutritional supplements appear in both *USP* and *NF*. USP intends to consolidate these monographs and *General Chapters* into one section of the third annual revision (2004). Excipient monographs usually are presented in *NF* but may also appear in *USP*, with suitable cross-referencing. A tabulation of excipients by functional category appears on page 2679.

Revisions—*USP–NF* is continuously revised. Revisions are presented annually, in twice-yearly *Supplements*, and in *Interim Revision Announcements* (*IRAs*).

Supplements—The *First Supplement* to *USP 26–NF 21* will be published in February 2003 and will become official in April 2003. The *Second Supplement* will be published in June 2003 and will become official in August 2003. Users of USP print products must retain both *Supplements* and keep their subscriptions current in order to have up-to-date information. The Index in each *Supplement* is cumulative and includes citations to the annual revision and, for the *Second Supplement*, citations to the *First Supplement*. The contents of the two *Supplements* are integrated into the annual edition of the following year.

Interim Revision Announcements—*IRAs* contain revisions that become official in the interval between publication of *Supplements*. They appear in USP's bimonthly journal, *Pharmacopeial Forum* (*PF*), with the official date noted in the publication. They are subsequently incorporated into the next *Supplement* or annual revision. One reprint of each *IRA* is available to *USP–NF* subscribers on request. Additional copies may be ordered from USP.

Pharmacopeial Forum—*PF* contains general information (Standards Development and Instructions for Use), Policies and Announcements, and *IRAs*. The following sections regularly appear in each issue of *PF*, in the order listed:

- How to Use *PF*
- Policies and Announcements
- *Interim Revision Announcements*
- In-Process Revision
- Previous *PF* Proposals Still Pending
- Canceled Proposals
- Harmonization
- Pharmacopeial Previews
- Stimuli to the Revision Process
- Nomenclature
- Index
- Reference Standards Catalog
- Order Form
- Intent to Comment Form
- Chromatographic Reagents Used in *USP–NF* and *PF*

The *Policies and Announcements* section provides information on publication and comment deadlines, scheduled meetings, USP news, and summaries of issues discussed by the Council of Experts and its Expert Committees. Proposals for revision are presented either as *Previews* or *In-Process Revisions*. Previews focus on monographs and *General Chapters* at an early stage of consideration. They also present new monographs for multi-source items and controversial items needing a longer public comment period. Depending on public comment, a Preview proposal may or may not advance to the In-Process Revision stage. In-Process Revisions represent final draft documents that are expected to advance to official status. *PF* also indicates Pending and Canceled Proposals, and provides a Harmonization section. The *Stimuli to the Revision Process* presents reports or statements of authoritative bodies, scientific articles relevant to compendial issues, general commentaries by interested parties, and summaries of comments received in response to policy initiatives. *PF* concludes with sections containing *Nomenclature*, *Index*, Reference Standards Catalog, Order and Comment Forms, and Chromatographic Reagents Used in *USP–NF* and *PF*. *PF* also provides a Cumulative index for a calendar year.

Reference Standards Catalog—The catalog listing the collection of official *USP–NF* Reference Standards is kept up-to-date through bimonthly publication in *PF*. It also can be accessed via the USP Home Page at www.usp.org. The listing identifies new items, replacement lots, lots of a single item that are simultaneously official, lots deleted from official status, and a preview of items eventually to be adopted. Purchase order information is included, and the names of distributors who can facilitate international availability of these items are suggested. This program benefits from the widespread voluntary contribution of suitable materials and test data from pharmaceutical manufacturers. Use of these *USP–NF* Reference Standards promotes uniform quality of drugs as an aid to the public health.

Chromatographic Reagents—This comprehensive reference provides detailed information needed to conduct chromatographic procedures found in *USP–NF*. *Chromatographic Reagents* lists the brand names of the column reagents cited in every proposal for new or revised gas- or liquid-chromatographic analytical procedures that have been published in *PF* since 1980. *Chromatographic Reagents* also helps to track which column reagents were used to validate analytical procedures that have become official. The branded column reagents list is updated bimonthly through *PF*.

Chemical Names and CAS Registry Numbers—The chemical subtitles given in the monographs are index names used by the Chemical Abstracts Service (CAS) of the American Chemical Society. They are provided only in monographs in which the titles specify substances that are distinctly definable chemical entities. The first subtitle is the inverted form of the systematic chemical name developed by the CAS. This is presented in accordance with the rules established over the years by the International Union of Pure and Applied Chemistry (IUPAC) and the International Union of Biochemistry, and is employed in the current issues of *Chemical Abstracts* (*CA*). The second subtitle, given in uninverted form, is of a systematic type formerly used in *CA*. It is identical with, or closely resembles, the chemical name sanctioned and employed by the IUPAC and by the World Health Organization (WHO). The IUPAC names make generous use of nonsystematic and semisystematic (often referred to as "trivial") names and qualifying terms, all of which impede electronic manipulation. In contrast, the CAS names are fully systematic for most substances and are amenable to search and retrieval. The two subtitles referred to above are frequently identical, and a CAS synonym is occasionally supplied as a third subtitle. Monographs with chemical subtitles generally also carry CAS registry numbers. These italicized, bracketed numbers function independently of nomenclature as invariant numerical designators of unique, unambiguous chemical substances in the CAS registry and thus find wide, convenient use.

Nomenclature—Names for ingredients are established through efforts of the United States Adopted Names (USAN) Council. USP participates in this activity together with the American Medical Association, the American Pharmaceutical Association, and the Food and Drug Administration (FDA). Drug product names can be established by FDA but more often are developed cooperatively with USP in activities of the Council of Experts' Nomenclature and Labeling Committee. Oversight of brand names is the responsibility of FDA, working with applicants. The USAN Council's program began in 1961 to provide ingredient names for drugs prior to their marketing. The Council's output is incorporated, along with other names for drugs (including generic, proprietary, and chemical names and code-designations), in the *USP Dictionary of USAN and International Drug Names*. Since 1988 this publication has been recognized by federal regulation as being the source of established names for drugs in the United States (see above). The USP Drug Nomenclature Committee was formed in 1986 to supplement the Executive Committees of the Drug Standards Division and the Information Division, and to prevent any inconsistency regarding nomenclature. Following the 2000 meeting of the USP Convention, the responsibility for devising and, where necessary, revising labeling requirements has been delegated to this Committee, which is now termed the Expert Committee on Nomenclature and Labeling. The Committee's work does not overlap that of the USAN Council. Rather, it is complementary and is concerned with standardization of compendial names, particularly dosage form names, and combination drug products.

USP Dictionary—*The USP Dictionary of USAN and International Drug Names* provides the most up-to-date United States Adopted Names of drugs; official *USP–NF* names; nonproprietary, brand, and chemical names; graphic formulas; molecular formulas and weights; CAS registry numbers and code designations; drug manufacturers; and pharmacologic and therapeutic categories—all in a single volume. The *Dictionary* helps to ensure the accuracy of product labeling; reports, articles, and correspondence; FDA regulatory filings; and pharmaceutical package inserts. It is published annually (last edition April 2002) and is recognized by FDA as the official source for established drug names.

Print and Electronic Presentations—All USP publications are available in print form. In addition, *USP–NF* and its two annual *Supplements* are available in compact disc (CD), intranet, and Internet versions. The CD version makes *USP–NF* accessible to users on their computer hard drives. The intranet format provides Web browser–based access to multiple users within an organization, through their own intranet server. Individual registered users can access the Internet or online format through the World Wide Web. All three electronic formats provide fast and easy access to official *USP–NF* content, along with extensive search options. The electronic formats are cumulatively updated to integrate the content of *Supplements*. An electronic version of *PF* is expected to be available by the end of 2002.

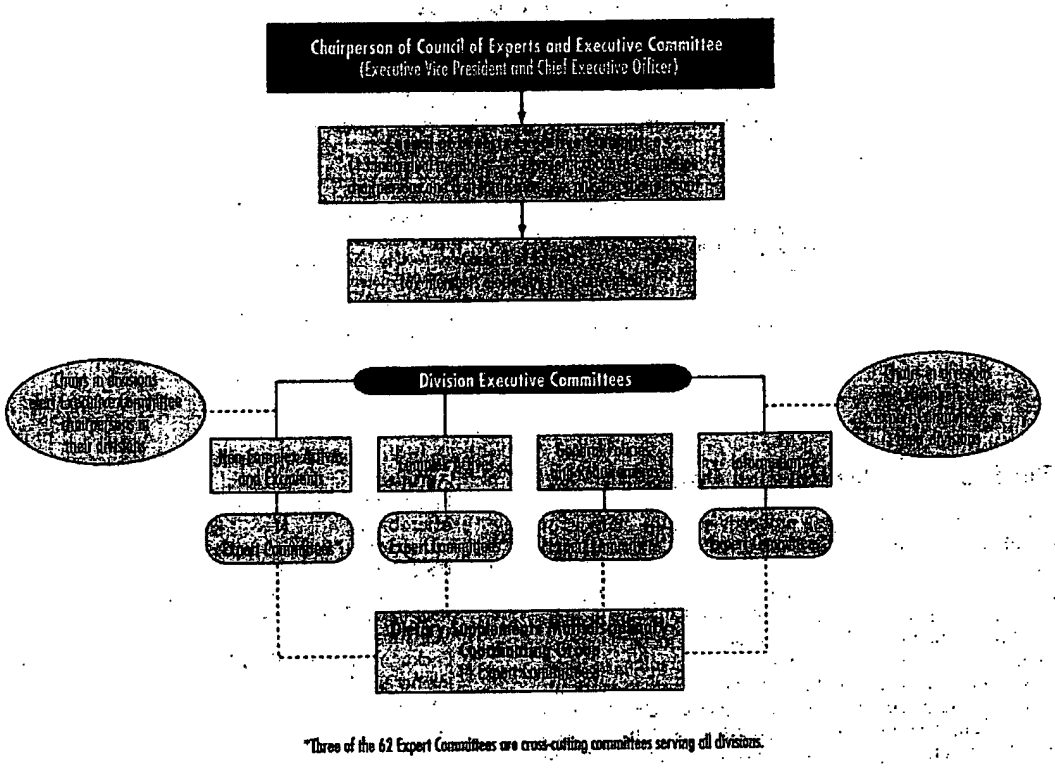
Symbols Indicating Change to Official Text—Symbols identify the beginning and end of each revision. For *Supplements*, a black square superscript marks the beginning of each revision, and a black square subscript marks the end. For the six yearly *Interim Revision Announcements*, black circles are used. Next to the subscript is a number that links the official date of the revision with the corresponding *Supplement* or *Interim Revision Announcement*. For example, a black square subscript with the numeral 1 next to it indicates that the revision will become official via the *First Supplement*. [NOTE—When *Interim Revision Announcements* are incorporated into the next *Supplement* or annual edition, the black circles will be replaced with

either the appropriate *Supplement* black square and number or annual edition triangle and number.] The following table shows symbols and official dates for *Interim Revision Announcements* and *Supplements* to *USP 26–NF 21:*

Supplement	Interim Revision Announcement	Official Date	Symbols
	1	February 1, 2003	• and ●1
1		April 1, 2003	■ and ■1
	2	April 1, 2003	• and ●2
	3	June 1, 2003	• and ●3
2		August 1, 2003	■ and ■2
	4	August 1, 2003	• and ●4
	5	October 1, 2003	• and ●5
	6	December 1, 2003	• and ●6

Revision Process

The Council of Experts—The Council of Experts is the standards-setting body of USP. It is composed of 62 Expert Committee chairs elected to five-year terms at USP's Convention in April 2000. A Nominating Committee, consisting of the Chair, Convention President, and the Vice-Chair of the Nominating Committee for the Council of Experts, proposes committee members who are subsequently elected by the members of the Council. The chairs and committee members consist of over 650 volunteers drawn from all parts of the world. The Expert Committees are organized into divisions (Figure 1), each of which has its own Executive Committee. The Council's Executive Committee provides overall direction, is an appeals body, and performs other functions that support the Council's operations. Thirty-one of the 62 Expert Committees create the content of *USP–NF* and associated publications (see below).



*Three of the 62 Expert Committees are cross-cutting committees serving all divisions.

Figure 1

Public Participation—While USP's Council of Experts is the ultimate decision-making body for *USP–NF* standards, these standards are developed by an exceptional process of public involvement and substantial interaction between USP and stakeholders (Figure 2). Proposals for drug monographs contain information submitted voluntarily by manufacturers and other interested parties. Via the *PF*, USP encourages public comment on these monographs and other draft documents. The Council of Experts reviews these responses and approves draft Proposals, which then become official in *USP–NF*. Thus, the USP standards-setting process gives those who manufacture, regulate, and use therapeutic products the opportunity to comment on the development and revision of *USP–NF* standards. The chart below shows the public review and comment process and its relationship to standards development.

Public Review and Comment Process for Standards Development

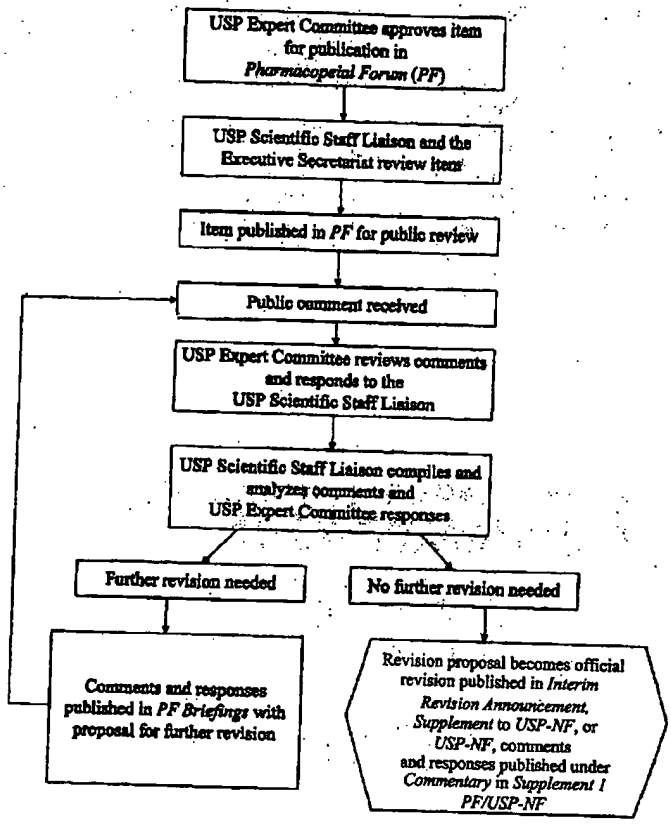


Figure 2

Participants in the Revision Process

Participation in the revision process proceeds with the support of many individuals and groups, and also from scientific, technical, and trade organizations.

Stakeholder Forums—In this five-year cycle, USP has formed several stakeholder forums as a means of enlisting the active participation of stakeholders interested in a specific area of focus. Depending on the topic, a stakeholder forum may form project teams to work more intensively on selected topics. As part of its efforts to work internationally with users of USP products and services, USP has also formed country-oriented communication groups. Following are lists of the stakeholder forums, project teams, and country communication groups.

STAKEHOLDER FORUMS

- Prescription/Non-Prescription
- Compounding
- Dietary Supplements

PROJECT TEAMS

- Drug Substance Monograph
- Complex Actives Drug Product Monograph
- Excipients
- Reference Standards Materials
- Dissolution Calibrator Tablets
- Drug Product Monographs–Biopharmaceutics
- Aerosols
- Pharmacy Compounding
- Microbiology
- Standardized Imprint Codes
- BSE/TSE
- Regulatory Guidances/General Chapters
- ICH/PDG Harmonization
- Statistics
- Packaging/Storage/Distribution
- Blood and Blood Products
- CPOE
- PAT

COMMUNICATION GROUPS

- India
- Brazil
- Mexico
- Canada
- Argentina
- Chile

Food and Drug Administration (FDA)—USP works with FDA in many ways to promote good communications and optimal interactions. Senior management of both organizations meet frequently throughout the year to provide oversight to these activities. FDA has formed an internal steering committee to review USP's work, while USP has formed task forces with interested FDA Centers. FDA's ad hoc reviewer program that places FDA representatives in Expert Committees allows continuing interactions between FDA

scientific staff and these Committees. Compendial staff in the Centers provide specific links and opportunities for exchange of comments. Current compendial staff contacts at FDA Centers are:

- Center for Veterinary Medicine (CVM): Stephen Sundloff, D.V.M., Ph.D.
- Center for Drug Evaluation and Research (CDER): Yana R. Mille
- Center for Food Safety and Applied Nutrition (CFSAN): Elizabeth A. Yetley, Ph.D.
- Office of Regulatory Affairs (ORA): Michael C. Olson, Ph.D.
- Center for Biological Evaluation and Research (CBER): Jerome A. Donlon, M.D., Ph.D.
- Center for Devices and Radiological Health (CDRH): Kiki B. Hellman, Ph.D.

Organizations—Revision of *USP–NF*, particularly in development of new monographs, General Chapters, and specifications for specialized products, continues to progress through the strong and proactive participation by manufacturers, compounding professionals, and many others. USP acknowledges the importance of this participation, which occurs through not only the Stakeholder forums but also through collaborative activities, work on project teams, and many other points of contact.

Staff—USP maintains a staff of approximately 320 scientifically-trained and other experts in its Rockville offices (see Figure 3). A primary activity of many of these staff members is to assist the Council of Experts in producing USP's publications (see Figure 4). A full listing of all USP employees is provided, beginning on page xviii after the names of Expert Committee members. Users of USP who have questions about the organization, its publications, USP Reference Standards, or general questions are referred to listings in *PF*, which are updated bimonthly.

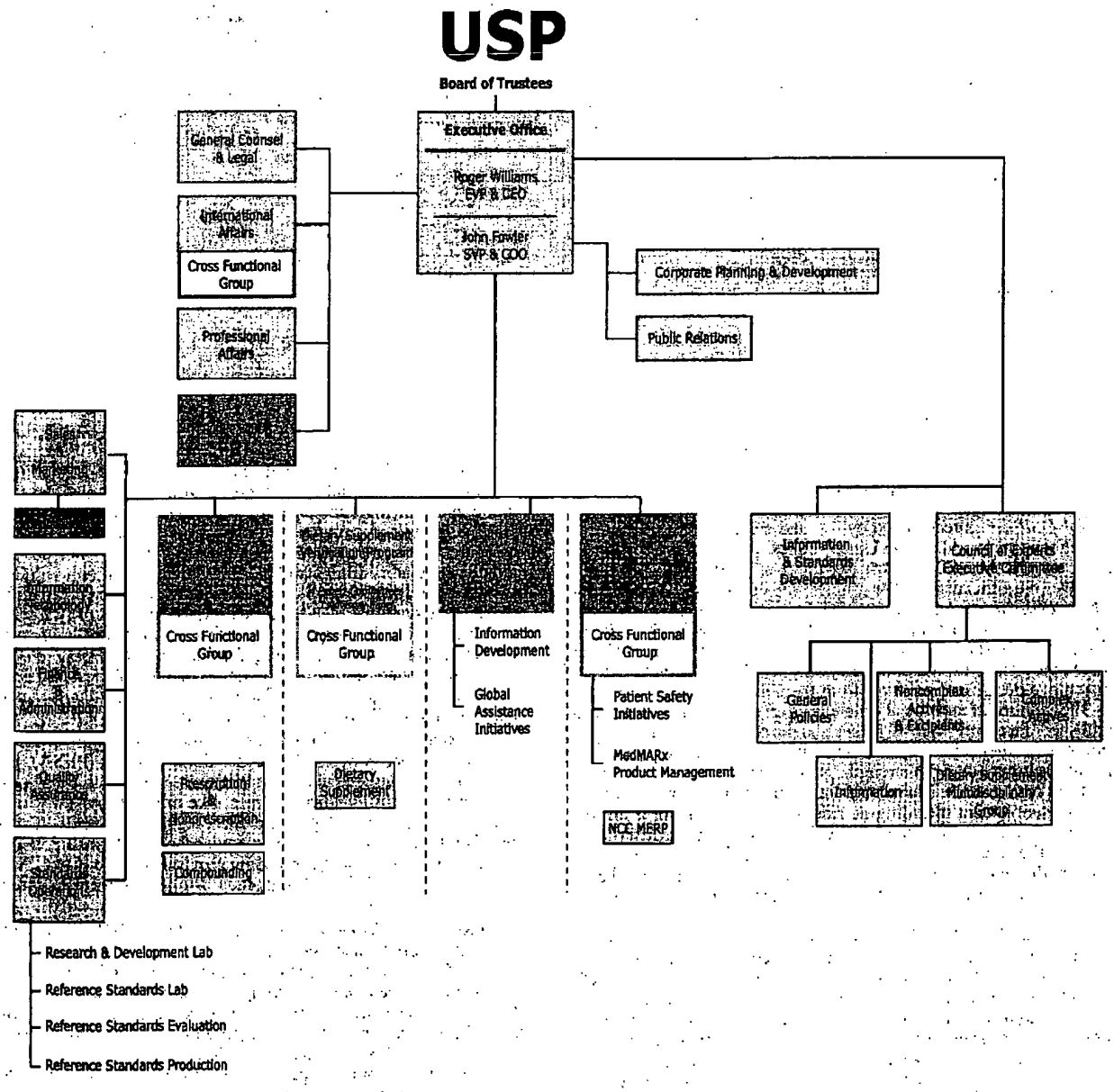


Figure 3

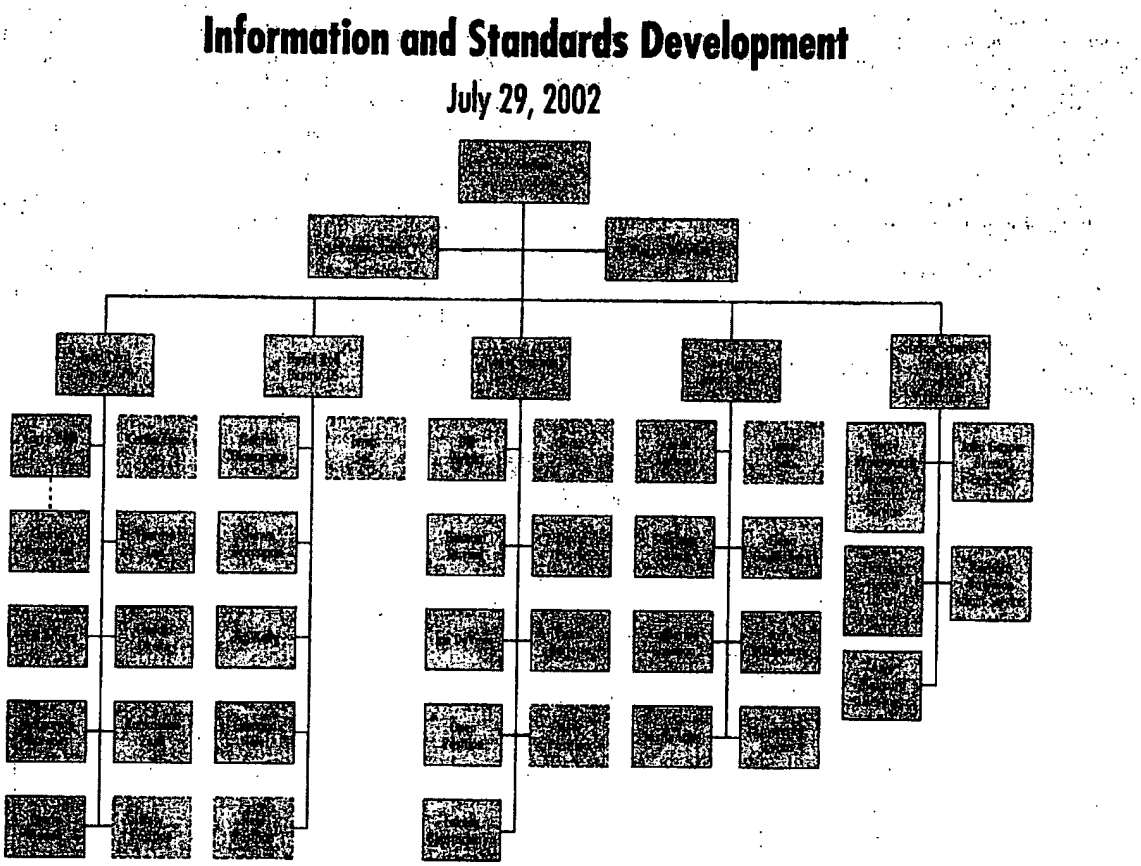


Figure 4

Legal Recognition

The *USP–NF* is recognized by law and custom in many countries throughout the world. In the United States, the Federal Food, Drug, and Cosmetic Act (FD&C Act) uses the term "official compendium" to mean the official *USP*, the official *NF*, the official *Homeopathic Pharmacopeia* of the United States, or any supplement to them. FDA may enforce compliance with official standards in *USP–NF* under the adulteration and misbranding provisions of the FD&C Act. These provisions extend broad authority to FDA to prevent entry to or remove designated products from the United States market.

The identity of an official article, as expressed by its name, is established if it conforms in all respects to the requirements of its monograph and other relevant portions of the compendia (e.g., *General Notices*). It may differ in strength, quality, or purity if the difference is stated on the article's label. Official preparations (a drug product, a dietary supplement including nutritional supplements, or a finished device) may contain additional suitable ingredients (see *General Notices*). Official drug products are prepared using ingredients that meet compendial monograph requirements when these monographs are provided, but they need not be prepared using only official ingredients.

Presence of a substance that causes an official article not to conform to the requirements of a monograph does not cause the article to be 'not USP.' Instead, the substance should be removed or a method developed that accounts for and controls its presence. If one of *USP's* analytical procedures is not suitable for a particular substance or product, a sponsor may submit a proposal for a different procedure, which could be incorporated into the relevant monograph and replace the prior procedure. A proposal for an alternative procedure might also be submitted. *USP* monographs are used for compliance. If a firm chooses non-*USP* procedures to demonstrate compliance, non-compliance for the U.S. market will still be assessed by FDA using the appropriate *USP* procedure. FDA can publish a different procedure in a regulation if it believes that a *USP* monograph procedure is deficient.

Drugs—USP's goal is to have substance and preparation (product) monographs for all FDA-approved drugs. USP also develops monographs for therapeutic products not approved by FDA; e.g., pre-1938 drugs and compounded preparations. The complex set of procedures that result in validation of private regulatory methods submitted in regulatory filings and the subsequent transition to a public official method in *USP–NF*, coupled with availability of a verified reference standard material, has been described elsewhere (T. Layloff, et.al., The U.S. FDA Regulatory Methods Validation Program for New and Abbreviated New Drug Applications, *Pharm. Tech.* and *Biopharm.*, January 2000). While submission of information needed to develop a monograph by the Council of Experts is voluntary, compliance with a *USP–NF* monograph, if available, is not.

Biologics—In the United States some biologics are regulated under the provisions of the Public Health Service Act (PHSA). Biologic products regulated under the PHSA are required to bear "proper" names not "established" names, like drugs. Provisions of the FD&C Act apply to biological products regulated under the PHSA. For this reason, products approved under the PHSA should comply with the adulteration and misbranding provisions of the FD&C Act at Section 501(b) and 502(g) and, thus, should conform to official monographs if available.

Medical Devices—Section 201(h) of the FD&C Act defines a device as an article/instrument, apparatus, or component recognized in the *USP–NF*. Section 502(e) defines the established name of a device in the absence of an FDA designation of the official name as the official title in an official compendium. Despite these statutory provisions, there is no comparable recognition of USP's standard-setting authority and ability to define the medical device as exists for other FDA-regulated therapeutic products. Under the Food and Drug Administration Modernization Act, CDRH recognizes national and international standards, including some *USP* tests and assays for medical devices.

Dietary Supplements—As with drugs and biologics, the Dietary Supplement Health and Education Act amendments to the FD&C Act name the *USP*, the *NF*, and the *Homeopathic Pharmacopeia* as

official compendia for dietary supplements. For this reason, a dietary supplement may be deemed misbranded if it is covered by the specifications in an official compendium, is represented as conforming to these specifications, and fails to conform. Therefore, the dietary supplement must assert conformance to the *USP–NF* monograph in order for the compendial standards to apply. Compliance with a *USP–NF* monograph is thus voluntary on the part of a dietary supplement manufacturer.

Compounded Preparations—Preparation monographs may also provide information or standards applicable in compounding. Compounding means the preparation, mixing, assembling, packaging, or labeling of a drug or device or other article, as the result of a practitioner's order or in anticipation of such an order based on routine, regularly-observed prescribing patterns. Standards in *USP–NF* for compounded preparations may be enforced at both the Federal and State levels.

Governance

Convention—USP's direction and priorities are determined by more than 400 credentialed Convention members divided into nine categories (page xxx). Within each membership category, eligible organizations are invited to appoint their representatives. Membership composition is determined to ensure suitable representation of those sections of the health care system that are impacted by, and in turn impact, USP's activities. D. Craig Brater, M.D., Dean of the Indiana University School of Medicine, is the USP Convention president for 2000-2005. Convention members elect USP's officers and trustees and the Council of Experts. They also vote on resolutions to guide USP's scientific policy and public health initiatives.

Board of Trustees—USP's Board of Trustees is entrusted with management of the business affairs, finances, and property of USP (Figure 5). During its five-year term, the Board defines USP's strategic direction through key policy and operational decisions.

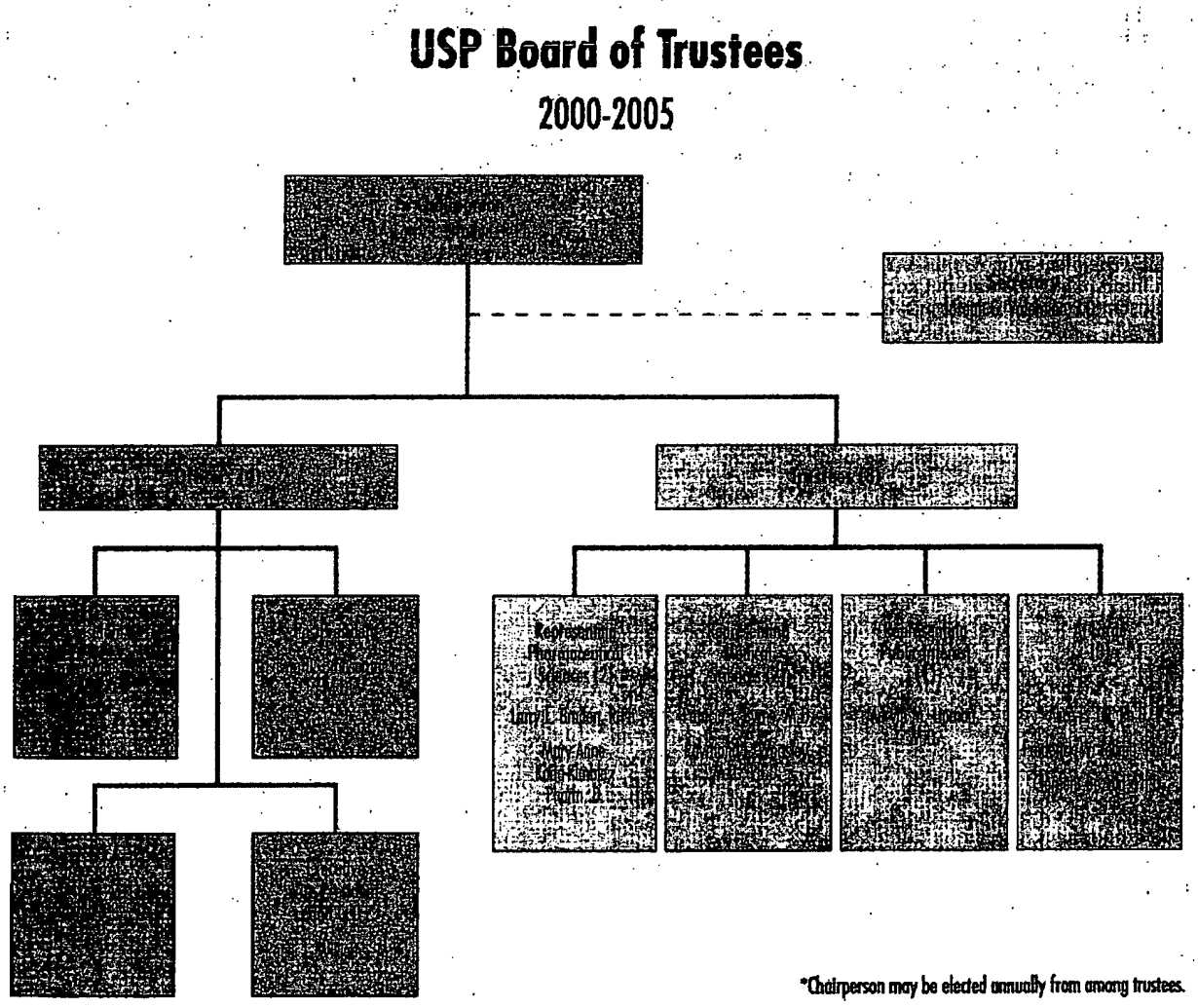


Figure 5

International Activities

World Health Organization (WHO)—USP works with the WHO in many of its normative and other activities that promote the availability of safe, effective, and good quality medicines. By invitation, USP staff participate as members or observers of WHO's expert advisory committees, including the Expert Committee on Pharmacuetical Preparations and the Biological Standards Expert Committees.

Pan American Health Organization (PAHO)—USP works with PAHO in many of its activities and has a six-year plan that is now in its fifth year of execution. USP participates actively in PAHO's Pan American Network for Drug Regulatory Harmonization (PANDRH). In this activity, USP attends meetings of the PANDRH Steering Committee as a non governmental observer (NGO). USP is coordinator for the Pharmacopoeial Working Group (PWG) and a member of the Bioavailability/Bioequivalence Working Groups in PANDRH. The PWG is composed of representatives from the Argentine, Brazilian, Mexican, and United States pharmacopeias, and receives direction from a Steering Committee, which was created at the third biennial PANDRH meeting in April 2002.

Pharmacopeial Discussion Group (PDG)—USP harmonizes pharmacopeial monographs and *General Chapters* in the PDG, which includes representatives from the European and Japanese pharmacopoeias, and WHO (observer). According to the PDG definition, a pharmacopoeial general chapter or other pharmacopoeial document is harmonized when a pharmaceutical substance or product tested by the procedure yields the same results, and the same accept/reject decision is reached. Harmonization for a particular monograph or General Chapter may be complete but more likely is partial. As an example, excipient monographs may be harmonized by attribute, which means that some tests but not others may be harmonized. Similarly, some General Chapters may be partially harmonized. Harmonization is not achieved until all active participants present official text in their pharmacopeias. Further information about the status of harmonization will be provided in a future chapter.

Country Activities—USP works internationally in individual countries to support compendial activities and other efforts that support the availability of safe, effective, and good-quality medicines. By means of a contract from the United States Agency for International Development, staff from USP's Global Assistance Initiatives program operates in many countries to support the availability of authoritative drug information and to provide approaches that help assure good-quality medicines.

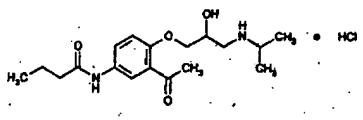
Miscellaneous

Fellowships and Internships—USP offers a number of year-long fellowships to doctoral candidates. A selection committee composed of USP Council of Experts members or Expert Committee Members evaluates candidates. Six awards for standards-related studies were made for the period of July 1, 2002 through June 30, 2003. The purpose of the USP Fellowships is to promote postgraduate research in areas related to compendial standards. Recognition is also given to sponsoring university faculty members elected to the USP Council of Experts or serving as a member of an Expert Committee or advisory panel. This year's fellows were selected from over 40 applicants.

USP also offers a number of summer internships to college students. Six interns were selected for summer 2002. These interns perform various duties at USP headquarters, which provide them with valuable experience working in areas related to USP's mission. This year's interns were selected from over 80 applicants.

Official Monographs for USP 26

Acebutolol Hydrochloride



$C_{18}H_{28}N_2O_4 \cdot HCl$ 372.89

Butanamide, *N*-[3-acetyl-4-[2-hydroxy-3-[(1-methylethyl)amino]-propoxy]phenyl]-, monohydrochloride, (±)-.

(±)-3′-Acetyl-4′-[2-hydroxy-3-(isopropylamino)propoxy]-butyranilide monohydrochloride [*34381-68-5*].

» Acebutolol Hydrochloride contains not less than 98.0 percent and not more than 102.0 percent of $C_{18}H_{28}N_2O_4 \cdot HCl$, calculated on the dried basis.

Packaging and storage—Preserve in tight containers.

USP Reference standards ⟨11⟩—*USP Acebutolol Hydrochloride RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: Prepare a mixture of the *Standard preparation* and the *Assay preparation* (1 : 1), and chromatograph the mixture as directed in the *Assay*: the chromatogram thus obtained exhibits a single major peak due to acebutolol.

C: It responds to the tests for *Chloride* ⟨191⟩, when tested as directed for alkaloidal hydrochlorides.

pH ⟨791⟩: between 4.5 and 7.0, in a solution (1 in 100).

Melting range ⟨741⟩: between 140° and 144°.

Loss on drying ⟨731⟩—Dry it at 105° for 3 hours: it loses not more than 1.0% of its weight.

Residue on ignition ⟨281⟩: not more than 0.1%.

Heavy metals, *Method II* ⟨231⟩: 0.002%.

Chromatographic purity—

Standard solution—Prepare a solution of USP Acebutolol Hydrochloride RS in methanol containing 1.0 mg per mL.

Test solution 1—Prepare a solution of Acebutolol Hydrochloride in methanol containing 10 mg per mL.

Test solution 2—Mix 1 mL of *Test solution 1* and 9 mL of methanol.

Reference solution 1—Transfer 3.0 mL of the *Standard solution* to a 100-mL volumetric flask, dilute with methanol to volume, and mix.

Reference solution 2—Mix 5.0 mL of *Reference solution 1* and 10.0 mL of methanol.

Procedure—Apply separate 20-µL portions of the *Standard solution*, *Test solution 1*, *Test Solution 2*, *Reference solution 1*, and *Reference solution 2* to a suitable thin-layer chromatographic plate (see *Thin-Layer Chromatography* under *Chromatography* ⟨621⟩) coated with a 0.25-mm layer of chromatographic silica gel mixture. Allow the spots to dry, and develop the chromatograms in a solvent system consisting of the upper layer of a mixture of water, butyl alcohol, and glacial acetic acid (50 : 40 : 10) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the plate to air-dry. Examine the plate under short-wavelength UV light: the chromatograms from *Test solution 2* and the *Standard solution* show principal spots at about the same R_F value. No secondary spot in the chromatogram from *Test solution 1*, excluding the area at the point of application, is more intense than the principal spot obtained from *Reference solution 1* (0.3%), and not more than two secondary spots in the chromatogram from *Test solution 1* are more intense than the principal spot obtained from *Reference solution 2* (0.1%), and the total of all impurities detected in the chromatogram of *Test solution 1* is not more than 0.5%.

Assay—

Mobile phase—Prepare a filtered and degassed mixture of methanol, a 0.3% aqueous solution of dodecyl sodium sulfate, and glacial acetic acid (675 : 325 : 20). Make adjustments if necessary to achieve a retention time for acebutolol of between 4 minutes and 7 minutes (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Acebutolol Hydrochloride RS quantitatively in water to obtain a solution having a known concentration of about 0.14 mg per mL.

Assay preparation—Transfer about 35 mg of Acebutolol Hydrochloride, accurately weighed, to a 250-mL volumetric flask, dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 3.9-mm × 30-cm column that contains packing L1. The flow rate is about 2 mL per minute. Chromatograph the *Standard preparation*, and record the peak responses as directed under *Procedure*: the column efficiency is not less than 1500 theoretical plates, the tailing factor is not more than 2.5, and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{18}H_{28}N_2O_4 \cdot HCl$ in portion of Acebutolol Hydrochloride taken by the formula:

$$250C(r_U/r_S),$$

in which C is the concentration, in mg per mL, of USP Acebutolol Hydrochloride RS in the *Standard preparation*, and r_U and r_S are the acebutolol peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively.

Acebutolol Hydrochloride Capsules

» Acebutolol Hydrochloride Capsules contain the equivalent of not less than 90.0 percent and not more than 110.0 percent of the labeled amount of acebutolol ($C_{18}H_{28}N_2O_4$).

Packaging and storage—Preserve in tight containers at a temperature not exceeding 30°.

USP Reference standards ⟨11⟩—*USP Acebutolol Hydrochloride RS.*

Identification—The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation*, as obtained in the *Assay*.

Dissolution ⟨711⟩—

Medium: water; 900 mL.

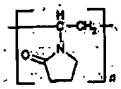
Apparatus 2: 50 rpm.

Time: 30 minutes.

Procedure—Determine the amount of $C_{18}H_{28}N_2O_4$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 232 nm on filtered portions of the solution under test in comparison with a Standard solution having a known concentration of USP Acebutolol Hydrochloride RS in the same *Medium*.

Tolerances—Not less than 80% (Q) of the labeled amount of acebutolol ($C_{18}H_{28}N_2O_4$) is dissolved in 30 minutes.

Povidone



$(C_6H_9NO)_n$

2-Pyrrolidinone, 1-ethenyl-, homopolymer.
1-Vinyl-2-pyrrolidinone polymer [*9003-39-8*].

Povidone is a synthetic polymer consisting essentially of linear 1-vinyl-2-pyrrolidinone groups, the degree of polymerization of which results in polymers of various molecular weights. It is characterized by its viscosity in aqueous solution, relative to that of water, expressed as a K-value, ranging from 10 to 120. The K-value of Povidone having a nominal K-value of 15 or less is not less than 85.0 percent and not more than 115.0 percent of the nominal K-value, and K-value of Povidone having a nominal K-value or nominal K-value range with an average of more than 15 is not less than 90.0 percent and not more than 108.0 percent of the nominal K-value or average of the nominal K-value range.

Packaging and storage—Preserve in tight containers.

Labeling—Label it to state, as part of the official title, the K-value or K-value range of the Povidone.

Identification—

A: To 10 mL of a solution (1 in 50) add 20 mL of 1 N hydrochloric acid and 5 mL of potassium dichromate TS: an orange-yellow precipitate is formed.

B: Dissolve 75 mg of cobalt nitrate and 300 mg of ammonium thiocyanate in 2 mL of water. To this solution add 5 mL of a solution of Povidone (1 in 50), and render the resulting solution acid by the addition of 3 N hydrochloric acid: a pale blue precipitate is formed.

C: To 5 mL of a solution (1 in 200) add a few drops of iodine TS: a deep red color is produced.

pH ⟨791⟩: between 3.0 and 7.0, in a solution (1 in 20).

Water, *Method I* ⟨921⟩: not more than 5.0%.

Residue on ignition ⟨281⟩: not more than 0.1%.

Lead ⟨251⟩—Dissolve 1.0 g in 25 mL of water: the limit is 10 ppm.

Limit of aldehydes—

Phosphate buffer—Transfer 50.0 g of potassium pyrophosphate to a 500-mL volumetric flask, and dissolve in 400 mL of water. Adjust, if necessary, with 1 N hydrochloric acid to a pH of 9.0, dilute with water to volume, and mix.

Aldehyde dehydrogenase solution—Transfer a quantity of lyophilized aldehyde dehydrogenase equivalent to 70 units to a glass vial, dissolve in 10.0 mL of water, and mix. [NOTE—This solution is stable for 8 hours at 4°.]

NAD solution—Transfer 40 mg of nicotinamide adenine dinucleotide to a glass vial, dissolve in 10.0 mL of *Phosphate buffer*, and mix. [NOTE—This solution is stable for 4 weeks at 4°.]

Standard preparation—Add about 2 mL of water to a glass weighing bottle, and weigh accurately. Add about 100 mg (about 0.13 mL) of freshly distilled acetaldehyde, and weigh accurately. Transfer this solution to a 100-mL volumetric flask. Rinse the weighing bottle with several portions of water, transferring each rinsing to the 100-mL volumetric flask. Dilute the solution in the 100-mL volumetric flask with water to volume, and mix. Store at 4° for about 20 hours. Pipet 1 mL of this solution into a 100-mL volumetric flask, dilute with water to volume, and mix.

Test preparation—Transfer about 2 g of Povidone, accurately weighed, to a 100-mL volumetric flask, dissolve in 50 mL of *Phosphate buffer*, dilute with *Phosphate buffer* to volume, and mix. Insert a stopper into the flask, heat at 60° for 1 hour, and cool to room temperature.

Procedure—Pipet 0.5 mL each of the *Standard preparation*, the *Test preparation*, and water to provide the reagent blank into separate 1-cm cells. Add 2.5 mL of *Phosphate* and 0.2 mL of *NAD solution* to each cell. Cover the cells to exclude oxygen. Mix by inversion, and allow to stand for 2 to 3 minutes at 22 ± 2°. Determine the absorbances of the solutions at a wavelength of 340 nm, using water as the reference. Add 0.05 mL of *Aldehyde dehydrogenase solution* to each cell. Cover the cells to exclude oxygen. Mix by inversion, and allow to stand for 5 minutes at 22 ± 2°. Determine the absorbances of the solutions at a wavelength of 340 nm, using water as the reference. Calculate the percentage of aldehydes, expressed as acetaldehyde, in the povidone taken by the formula:

$$10(C/W)\left[\frac{(A_{U2}-A_{U1})-(A_{B2}-A_{B1})}{(A_{S2}-A_{S1})-(A_{B2}-A_{B1})}\right]$$

in which C is the concentration, in mg per mL, of acetaldehyde in the *Standard preparation*, W is the weight, in g, of Povidone taken; A_{U1}, A_{S1}, and A_{B1} are the absorbances of the solutions obtained from the *Test preparation*, the *Standard preparation*, and the water reagent blank, respectively, before addition of the *Aldehyde dehydrogenase solution*; and A_{U2}, A_{S2}, and A_{B2} are the absorbances of the solutions obtained from the *Test preparation*, the *Standard preparation*, and the water reagent blank, respectively, after addition of the *Aldehyde dehydrogenase solution*: not more than 0.05% is found.

Limit of hydrazine—Transfer 2.5 g to a 50-mL centrifuge tube, add 25 mL of water, and mix to dissolve. Add 500 µL of a 1 in 20 solution of salicylaldehyde in methanol, swirl, and heat in a water bath at 60° for 15 minutes. Allow to cool, add 2.0 mL of toluene, insert a stopper in the tube, shake vigorously for 2 minutes, and centrifuge. Apply 10 µL of the clear upper toluene layer in the centrifuge tube and 10 µL of a Standard solution of salicylaldazine in toluene containing 9.38 µg per mL to a suitable thin-layer chromatographic plate (see *Chromatography* ⟨621⟩) coated with a 0.25-mm layer of dimethylsilanized chromatographic silica gel mixture. Allow the spots to dry, and develop the chromatogram in a solvent system consisting of a mixture of methanol and water (2:1) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Locate the spots on the plate by examination under UV light at a wavelength of 365 nm: salicylaldazine appears as a fluorescent spot having an R_f value of about 0.3, and the fluorescence of any salicylaldazine spot from the test specimen is not more intense than that produced by the spot obtained from the Standard solution (1 ppm of hydrazine).

Vinylpyrrolidinone—Dissolve 10.0 g of Povidone in 80 mL of water, add 1.0 g of sodium acetate, and titrate with 0.10 N iodine until the color of iodine no longer fades. Add an additional 3.0 mL of 0.10 N iodine, allow to stand for 10 minutes, and titrate the excess iodine with 0.10 N sodium thiosulfate, adding 3 mL of starch TS as the endpoint is approached. Perform a blank determination (see *Residual Titrations* under *Titrimetry* ⟨541⟩), using the same total volume of 0.10 N iodine, accurately measured, as was used for titrating the specimen: not more than 3.6 mL of 0.10 N iodine is consumed, corresponding to not more than 0.2% of vinylpyrrolidinone.

K-value—Weigh accurately a quantity of undried Povidone equivalent on the anhydrous basis to the amount specified in the following table:

Nominal K-value	g
≤18	5.00
>18 to ≤95	1.00
>95	0.10

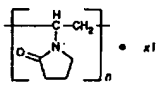
Dissolve it in about 50 mL of water in a 100-mL volumetric flask, dilute with water to volume, and mix. Allow to stand for 1 hour. Determine the viscosity, using a capillary-tube viscosimeter (see *Viscosity* ⟨911⟩) of this solution at 25 ± 0.2°. Calculate the K-value of Povidone by the formula:

$$[\sqrt{300c \log z + (c + 1.5c \log z)^2} + 1.5c \log z - c]/(0.15c + 0.003c^2)$$

in which c is the weight, in g, on the anhydrous basis, of the specimen tested in each 100.0 mL of solution, and z is the viscosity of the test solution relative to that of water.

Nitrogen content—Proceed as directed under *Nitrogen Determination, Method II* ⟨461⟩, using about 0.1 g of Povidone, accurately weighed. In the procedure, omit the use of hydrogen peroxide, use 5 g of a powdered mixture of potassium sulfate, cupric sulfate, and titanium dioxide (33 : 1 : 1), instead of potassium sulfate and cupric sulfate (10 : 1), and heat until a clear, light-green solution is obtained, then heat for a further 45 minutes: the nitrogen content, on the anhydrous basis, is not less than 11.5% and not more than 12.8%.

Povidone-Iodine



$(C_6H_9NO)_n \cdot xI$

2-Pyrrolidinone, 1-ethenyl-, homopolymer, compd. with iodine.
1-Vinyl-2-pyrrolidinone polymer, compound with iodine
[*25655-41-8*].

» Povidone-Iodine is a complex of Iodine with Povidone. It contains not less than 9.0 percent and not more than 12.0 percent of available iodine (I), calculated on the dried basis.

Packaging and storage—Preserve in tight containers.

Identification—

A: Add 1 drop of a solution (1 in 10) to a mixture of 1 mL of starch TS and 9 mL of water: a deep blue color is produced.

B: Spread 1 mL of a solution (1 in 10) over an area of about 20 cm × 20 cm on a glass plate, and allow to air-dry at room temperature in an atmosphere of low humidity overnight: a brown, dry, non-smearing film is formed, and it dissolves readily in water.

Loss on drying ⟨731⟩—Dry 5.0 g of it at 105° until the difference between two successive weighings at 1-hour intervals is not greater than 5.0 mg: it loses not more than 8.0% of its weight.

Residue on ignition ⟨281⟩: negligible, from 2 g.

Iodide ion—

Determination of total iodine—Dissolve about 500 mg of Povidone-Iodine, accurately weighed, in 100 mL of water in a 250-mL conical flask. Add sodium bisulfite TS until the color of iodine has disappeared. Add 25.0 mL of 0.1 N silver nitrate VS and 10 mL of nitric acid, and mix. Titrate the excess silver nitrate with 0.1 N ammonium thiocyanate VS, using ferric ammonium sulfate TS as the indicator. Perform a blank determination (see *Residual Titrations* under *Titrimetry* ⟨541⟩). Each mL of 0.1 N silver nitrate is equivalent to 12.69 mg of I. From the percentage of total iodine, calculated on the dried basis, subtract the percentage of available iodine (see *Assay for available iodine*), to obtain the percentage of iodide ion. Not more than 6.6%, calculated on the dried basis, is found.

Heavy metals, *Method II* ⟨231⟩: 0.002%.

Nitrogen content ⟨461⟩—Not less than 9.5% and not more than 11.5% of N is found, calculated on the dried basis.

Assay for available iodine—Place about 5 g of Povidone-Iodine, accurately weighed, in a 400-mL beaker, and add 200 mL of water. Cover the beaker, and stir by mechanical means at room temperature for not more than 1 hour to dissolve as completely as possible. Titrate immediately with 0.1 N sodium thiosulfate VS, adding 3 mL of starch TS as the endpoint is approached. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N sodium thiosulfate is equivalent to 12.69 mg of I.

Povidone-Iodine Topical Aerosol

Former title: Povidone-Iodine Topical Aerosol Solution

» Povidone-Iodine Topical Aerosol is a solution of Povidone-Iodine under nitrogen in a pressurized container. It contains not less than 85.0 percent and not more than 120.0 percent of the labeled amount of iodine (I).

Packaging and storage—Preserve in pressurized containers, and avoid exposure to excessive heat.

Identification—Spray Topical Aerosol into a beaker or flask until about 50 mL has been collected, and allow to stand for 5 minutes to allow the entrapped propellant to escape. (Retain portions of the solution so obtained for the *pH* and *Assay* procedures.) The solution meets the requirements of the following tests.

A: Add 1 mL of a dilution containing about 0.05% of iodine to a mixture of 1 mL of starch TS and 9 mL of water: a deep blue color is produced.

B: Transfer 10 mL to a 50-mL conical flask, avoiding contact with the neck of the flask. Cover the mouth of the flask with a small disk of filter paper, and wet it with 1 drop of starch TS: no blue color appears within 60 seconds.

pH ⟨791⟩—The pH of the solution prepared for the *Identification* tests is not more than 6.0.

Other requirements—It meets the requirements for *Pressure Test*, *Minimum Fill*, and *Leakage Test* under *Aerosols, Metered-Dose Inhalers, and Dry Powder Inhalers* ⟨601⟩.

Assay—Transfer an accurately measured volume of the solution of Topical Aerosol prepared for the *Identification* tests, equivalent to about 50 mg of iodine, to a 100-mL beaker, and dilute with water to a total volume of not less than 30 mL. Titrate immediately with 0.02 N sodium thiosulfate VS, determining the endpoint potentiometrically, using a platinum-calomel electrode system. Perform a blank determination, and make any necessary correction. Each mL of 0.02 N sodium thiosulfate is equivalent to 2.538 mg of iodine (I).

Povidone-Iodine Ointment

» Povidone-Iodine Ointment is an emulsion, solution, or suspension of Povidone-Iodine in a suitable water-soluble ointment base. It contains not less than 85.0 percent and not more than 120.0 percent of the labeled amount of iodine (I).

Packaging and storage—Preserve in tight containers.

Identification—

A: Add 1 mL of an alcohol dilution of it containing about 0.05% of iodine to a mixture of 1 mL of starch TS and 9 mL of water: a deep blue color is produced.

B: Place 10 g in a 50-mL beaker, avoiding contact with the walls of the beaker. Cover the mouth of the beaker with a disk of filter paper, and wet it with 1 drop of starch TS: no blue color appears within 60 seconds.

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U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

INFORMATION DISCLOSURE STATEMENT		Docket Number: **1662/51303**	
Application Number 10/071,423	Filing Date February 8, 2002	Examiner Not Assigned	Art Unit
Invention Title A STABLE PHARMACEUTICAL FORMULATION COMPRISING TORSEMIDE MODIFICATION II		Inventors **LEIBOVICI et al.**	

Address to:
Assistant Commissioner for Patents
Washington D.C. 20231

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231 on

Date: 5/28/02 Reg. No. 46,877

Signature: Siu K Lo

1. In accordance with the duty of disclosure under 37 C.F.R. § 1.56 and in conformance with the procedures of 35 U.S.C. §§ 1.97 and 1.98 and M.P.E.P. § 609, attorneys for Applicants hereby bring the following references to the attention of the Examiner. These references are listed on the attached modified PTO Form No. 1449. It is respectfully requested that the information be expressly considered during the prosecution of this application, and that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

2. Copies of each patent, publication or other information listed on the modified PTO form 1449 are not enclosed since they were previously cited by or submitted to the Patent Office in prior application Serial No. 09/789,424, which is relied upon for an earlier filing date under 35 U.S.C. 120.

Dated: 5/28/02

By: Siu K Lo

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT	ATTY. DOCKET NO. 1662/51303	SERIAL NO.
	APPLICANT LEIBOVICI et al.	
	FILING DATE Feb. 8, 2002	GROUP

U. S. PATENT DOCUMENTS

EXAMINER INITIAL	PATENT NUMBER	PATENT DATE	NAME	CLASS	SUBCLASS	FILING DATE*
	Re. 30,633	June 2, 1981	Delarge et al.			
	Re. 34,672	Jul. 26, 1994	Topfmeier et al.			
	4,822,807	April 18, 1989	Topfmeier et al.			
	5,738,872	April 14, 1998	Ortyl et al.			
	5,914,336	June 22, 1999	Dreckmann-Behrendt			

* - If pertinent

FOREIGN PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
						YES	NO

OTHER DOCUMENTS

EXAMINER INITIAL		AUTHOR, TITLE, DATE, PERTINENT PAGES, ETC.
		Acta Crystallographica, Vol. B34 Part 4, 15 April 1978 (pp.1051-1400).
		Acta Crystallographica, Vol. B34 Part 8, 15 August 1978 (pp.2387-2672).

EXAMINER	DATE CONSIDERED
EXAMINER: Initial if citation considered, whether or not citation is in conformance with M.P.E.P. 609; draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.	